Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

FEBRUARY--1958
Volume 8 — Number 2

a first on the list *

Artane

HYDROCHLORIDE TRIHEXYPHENIDYL HCl LEDERLE

ARTANE is effective in all forms of Parkinsonism, cardiac, hypertensive, postencephalitic and idiopathic types. Well tolerated, ARTANE maintains strong antispasmodic action over prolonged periods of treatment. ARTANE is remarkably free of serious toxic properties, has no deleterious effect on bone marrow function.

Supplied: 2 mg. and 5 mg. tablets, and elixir containing 2 mg. per teaspoonful (5 cc.)

Dosage: 1 mg. the first day, gradually increased, according to response, to 6 mg. to 10 mg. daily divided in 3 doses at mealtime.

*Reg. U.S. Pat. Off.

Lederle

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK

facilitates management of the psychotic...

Trilafon*

(pronounced Trill'-ah-fon) perphenazine

full-range tranquilization

- At least five times more potent than earlier phenothiazines
- Skin rashes and nasal congestion uncommon
- Jaundice notably infrequent in studies to date
- Significant hypotension virtually absent
- Mild insomnia and motor restlessness infrequent

TO REACH THE "INACCESSIBLE" PSYCHOTIC

- Reduces psychomotor overactivity
- Useful adjuvant to shock therapy—markedly reduces postshock anxiety and excitement
- Facilitates more rapid transfer to convalescent status

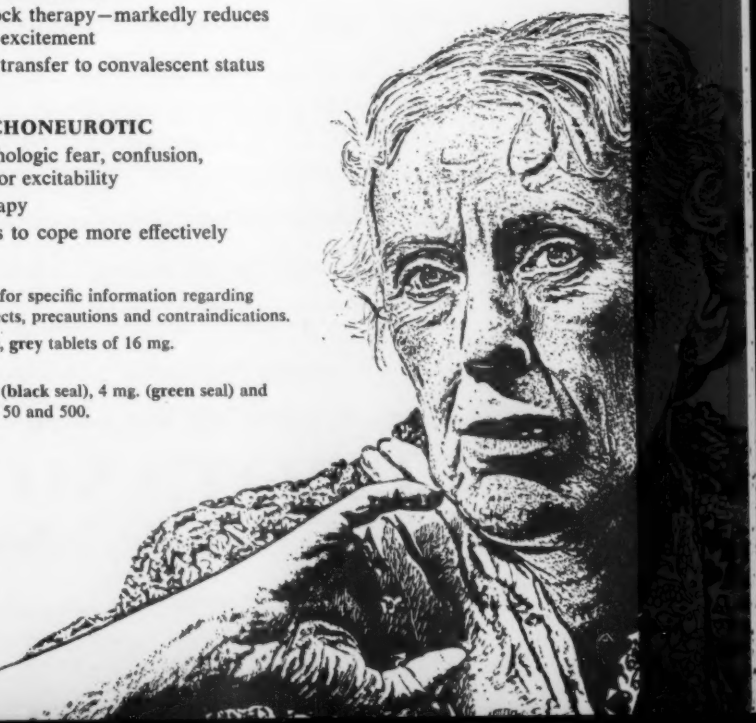
TO SUPPORT THE PSYCHONEUROTIC

- TRILAFON—quiets pathologic fear, confusion, irritability, psychomotor excitability
- Facilitates psychotherapy
- Helps psychoneurotics to cope more effectively with reality

Refer to Schering literature for specific information regarding indications, dosage, side effects, precautions and contraindications.

TRILAFON—For hospital use, grey tablets of 16 mg. (red seal), bottle of 500.

Also—grey tablets of 2 mg. (black seal), 4 mg. (green seal) and 8 mg. (blue seal), bottles of 50 and 500.



Schering

SCHERING CORPORATION
BLOOMFIELD, NEW JERSEY

*T.M. TR-J-3197

"Doctors can't help shingles?"

Physicians who have used PROTAMIDE extensively deplore such statements as unfortunate when they appear in the lay press. They have repeatedly observed in their practice quick relief of pain, even in severe cases, shortened duration of lesions, and greatly lowered incidence of postherpetic neuralgia when PROTAMIDE was started promptly. A folio of reprints is available. These papers report on zoster in the elderly—the severely painful cases—patients with extensive lesions. PROTAMIDE users know "shingles" *can* be helped.

PROTAMIDE®

Sherman Laboratories

Detroit 11, Michigan

Available: Boxes of 10 ampuls—prescription pharmacies.

Volume 8 **Neurology** *Number 2*

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

OFFICERS

FRANCIS M. FORSTER, M.D., *President*

AUGUSTUS S. ROSE, M.D., *President-Elect*

A. L. SAHS, M.D., *Vice-President*

JOSEPH M. FOLEY, M.D., *Secretary*

CHARLES VAN BUSKIRK, M.D., *Treasurer*

BOARD OF EDITORS

Editor-in-Chief: RUSSELL N. DEJONG, M.D., *Ann Arbor, Michigan*

Associate Editor: MABEL G. MASTEN, M.D., *Miami, Florida*

Editorial Board: PEARCE BAILEY, M.D., *Washington, D. C.*

JOE R. BROWN, M.D., *Rochester, Minnesota*

ROLAND P. MACKAY, M.D., *Chicago, Illinois*

H. HOUSTON MERRITT, M.D., *New York, New York*

JAMES L. O'LEARY, M.D., *St. Louis, Missouri*

E. P. RICHARDSON, JR., M.D., *Boston, Massachusetts*

RICHARD B. RICHTER, M.D., *Chicago, Illinois*

J. PRESTON ROBB, M.D., *Montreal, Canada*

DONALD B. TOWER, M.D., *Bethesda, Maryland*

ALPHONSE R. VONDERAHE, M.D., *Cincinnati, Ohio*

A. EARL WALKER, M.D., *Baltimore, Maryland*

PAUL I. YAKOVLEV, M.D., *Boston, Massachusetts*

NEUROLOGY is published monthly at 84 South Tenth Street, Minneapolis 3, Minnesota, by LANCET PUBLICATIONS, INCORPORATED. Subscription rate: $12.00 a year, $1.00 a copy; outside the United States $13.00 a year, $1.10 a copy. Entered as second class matter at the postoffice at Minneapolis, January 23, 1951.

"MYSOLINE"®

Brand of Primidone

in epilepsy

Reports from 15 countries attest to the clinical effectiveness of "Mysoline" in grand mal and psychomotor attacks. These results are confirmed by three years of successful use in the United States. No irreversible toxic effects have been reported. When side effects such as drowsiness and ataxia occur, they are usually mild and transitory, tending to disappear as therapy is continued or dosage is adjusted.

Supplied: 0.25 Gm. scored tablets, bottles of 100 and 1,000.

Ayerst

AYERST LABORATORIES • NEW YORK, N. Y. • MONTREAL, CANADA

"Mysoline" is available in the United States by arrangement with Imperial Chemical Industries Ltd.

5760

Volume 8 **Neurology** Number 2

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

FEBRUARY 1958 • *Contents*

Arteriovenous Anomalies of the Brain
A Review and Presentation of 37 Cases 89
FRANK M. ANDERSON, M.D. AND MARVIN A. KORBIN, M.D.

Prolonged Effects of Reticular Formation Stimulation on Reflex Action 102
KIYOMI KOIZUMI, M.D., ISAMU SUDA, M.D. AND CHANDLER McC. BROOKS, Ph.D.

Alterations in Blood Gases During Natural Sleep and Narcolepsy
A Correlation with the Electroencephalographic Stages of Sleep 107
RICHARD I. BIRCHFIELD, M.D., HERBERT O. SIEKER, M.D. AND ALBERT HEYMAN, M.D.

Experimental In Vitro Demyelination 113
ALBERT SCHATZ, Ph.D. AND LIONEL M. ADELSON, M.S.

Clinical Significance of Impairment of Sound Localization 119
LUIS P. SANCHEZ-LONGO, M.D. AND FRANCIS M. FORSTER, M.D.

Dilantin in the Treatment of Trigeminal Neuralgia 126
ANTHONY IANNONE, M.D., A. B. BAKER, M.D. AND FRANK MORRELL, M.D.

A Study on Traumatic Lumbar Punctures 129
WALLACE W. TOURTELLOTTE, Ph.D., M.D., JOHN F. SOMERS, M.D., JULIUS A. PARKER, A.B., HIDEO H. ITABSHI, M.D. AND RUSSELL N. DE JONG, M.D.

Caudate Lesions and Spontaneous Locomotion in the Monkey 135
GEORGE D. DAVIS, Ph.D.

(Continued on next page)

NEUROLOGY, copyright 1958 by LANCET PUBLICATIONS, INCORPORATED. Title registered United States Patent Office. Louis M. Cohen, Publisher. Margaret M. Kane, Managing Editor. Maurice Wolff, Business Manager. 84 S. Tenth St., Minneapolis 3, Minn. ADVERTISING REPRESENTATIVES: *New York 17:* Lee Klemmer, Bernard A. Smiler, John Winter, 1 E. 42nd St. Telephone: Murray Hill 2-8717. *Chicago 6:* Jay H. Herz, Hugh Gibson, 20 N. Wacker Drive, Suite 1921. Telephone: Central 6-4619. *San Francisco 4:* Duncan A. Scott & Co., Mills Bldg. Telephone: Garfield 1-7950. *Los Angeles 57:* Duncan A. Scott & Co., 1901 West Eighth St. Telephone: Dunkirk 8-4151.

Contents — *Continued*

Effect of Diphenylhydantoin on Peripheral Nerve 140
FRANK MORRELL, M.D., WILLIAM BRADLEY, M.D. AND MARK PTASHNE

Occlusion of the Basilar Artery
A Clinical and Pathologic Study of 14 Autopsied Cases 145
HUMBERTO CRAVIOTO, M.D., J. REY-BELLET, M.D.,
PHILIP H. PROSE, M.D. AND IRWIN FEIGIN, M.D.

Case Report
Intrathoracic Meningocele 153
PAUL TENG, M.D. AND PETER EASTMAN, M.D.

INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

Manuscripts submitted for publication (other than those read at meetings of the Academy) should be sent to Dr. Russell N. DeJong, University Hospital, Ann Arbor, Michigan. Books for review and business correspondence should be addressed to NEUROLOGY, 84 South Tenth Street, Minneapolis 3, Minnesota. News items related to the American Academy of Neurology or to the field of neurology in general are to be sent to Dr. Pearce Bailey, 4725 Sedgwick, N.W., Washington 16, D.C.

Manuscripts are accepted for publication on condition that they are contributed solely to NEUROLOGY. They must be typewritten, double spaced, and only the original copy should be submitted. Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be glossy prints. Tables should be typed on separate sheets. The title of the article, name of author, and number of figure should be placed on the back of every illustration, and the top should be designated. Legends for figures should be typed and are not to be attached to the illustrations. If the number of illustrations or tables is excessive, the author will be asked to defray a part of the cost.

References should be designated in the text by superior number, and should be listed at the end of the article in numerical sequence. They should be typed in the following manner:

Journal reference: 1. FRANKLIN, C. R., and BRICKNER, R. M.: Vasospasm associated with multiple sclerosis. Arch. Neurol. & Psychiat. 58:125, 1947.

Textbook reference: 2. WECHSLER, I. S.: A Textbook of Clinical Neurology, ed. 3. Philadelphia, W. B. Saunders Company, 1935, pp. 194-199.

Abbreviations should follow the style of the Quarterly Cumulative Index Medicus.

Galley proofs will be sent to authors for prompt correction. There will be no charge for corrections unless excessive alterations are made. A schedule of charges for reprints will accompany the galley proof.

Psychiatrists

Pacatal produces "a remarkable fluidity and warmness of affect."[1]

Patients

Pacatal makes me feel "'on top of the world' and wonderfully clear in the head."[2]

Personnel

With Pacatal "the hospital atmosphere is calmer and more optimistic . . . work more interesting."[3]

. . . agree on the euphoric effect of

Pacatal®

(BRAND OF MEPAZINE)

Pacatal is distinguished from the earlier phenothiazine compounds because it does not "flatten" the patient. Pacatal leaves him alert and cheerful—more responsive to your therapy. Side effects, too, are fewer; and when they do occur, are usually quickly controlled or reversed.

Dosage: Usual dosage for the hospitalized patient is 50 mg. 3 or 4 times daily; for the ambulant patient, 25 mg. 3 or 4 times daily. *Complete literature and dosage instructions, available on request, should be consulted.*

Supplied: 25 and 50 mg. tablets in bottles of 100 and 500; 100 mg. tablets in bottles of 500. Also available in 2 cc. ampuls (25 mg./cc.) for parenteral use.

References:
1. Sainz, A.: Personal communication.
2. Hutchinson, J. T.: Evaluation of Pacatal in Psychotic States, address before the American Psychiatric Association, Nov. 16, 1956.
3. Bowes, H. A.: Am. J. Psychiat. *113*:530 (Dec.) 1956.

back from the brink with **Pacatal®**

WARNER-CHILCOTT

100 YEARS OF SERVICE TO THE MEDICAL PROFESSION

UNIQUE Robins ***research discovery***

for SELECTIVE, SUPERIOR

skeletal muscle relaxation

ROBAXIN—a completely new chemical formulation—provides sustained relaxation of skeletal muscle spasm, without impairment of muscle strength or normal neuromuscular function . . . and with essential freedom from adverse side effects. Beneficial in 94.4% of cases tested.

Robaxin®

METHOCARBAMOL "ROBINS", U.S. PAT. NO. 2770569

Supply:
Tablets, 0.5 Gm., bottles of 50.

A. H. ROBINS CO., INC., *Richmond 20, Virginia*
Ethical Pharmaceuticals of Merit since 1878

'Thorazine' Spansule capsules are excellent for the discharged mental patient

'Thorazine' *Spansule* capsules provide all-day maintenance therapy with a single dose taken in the morning. Discharged patients are saved the embarrassment of taking medicine at work, and the risk of forgotten midday doses is eliminated.

Most important of all, the continuous medication provided by 'Thorazine' *Spansule* capsules helps the discharged patient deal with the stress situations he encounters so frequently during his rehabilitation.

'Thorazine' *Spansule* capsules are offered in four strengths: 30 mg., 75 mg., 150 mg. and 200 mg.

THORAZINE* chlorpromazine, S.K.F.

SPANSULE* sustained release capsules, S.K.F.

Smith Kline & French Laboratories, Philadelphia 1

first ⧗ in sustained release oral medication

*T.M. Reg. U.S. Pat. Off.

REVIEW COURSES IN
BASIC and CLINICAL NEUROLOGY

APRIL 21, 22, 23, 1958

Preceding the

1958 AMERICAN ACADEMY OF NEUROLOGY MEETING

Bellevue-Stratford Hotel, Philadelphia, Pennsylvania

NEUROPATHOLOGY—April 21, 1958. Dr. Erland R. Nelson. Fees: Juniors $15.00; Fellows, Actives, and Associates: $20.00; Non-members: $30.00. Deposit on slide box: $25.00 (all membership categories).

DISORDERS OF MOVEMENT—April 21, 1958. Dr. Charles A. Kane. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

NEUROPHARMACOLOGY—April 21, 1958. Dr. Donald B. Tower. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

ELECTROENCEPHALOGRAPHY—April 22, 1958. Dr. Frank Morrell. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

PEDIATRIC NEUROLOGY—April 22, 1958. Dr. Sidney Carter. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

PHYSIOLOGY AND DISEASES OF CEREBRAL CIRCULATION—April 22, 1958. Dr. A. L. Sahs. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

CURRENT ADVANCES IN NEUROLOGY—April 23, 1958. Dr. Joe R. Brown. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

NEURO-OPHTHALMOLOGY—April 23, 1958. Dr. N. S. Schlezinger. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

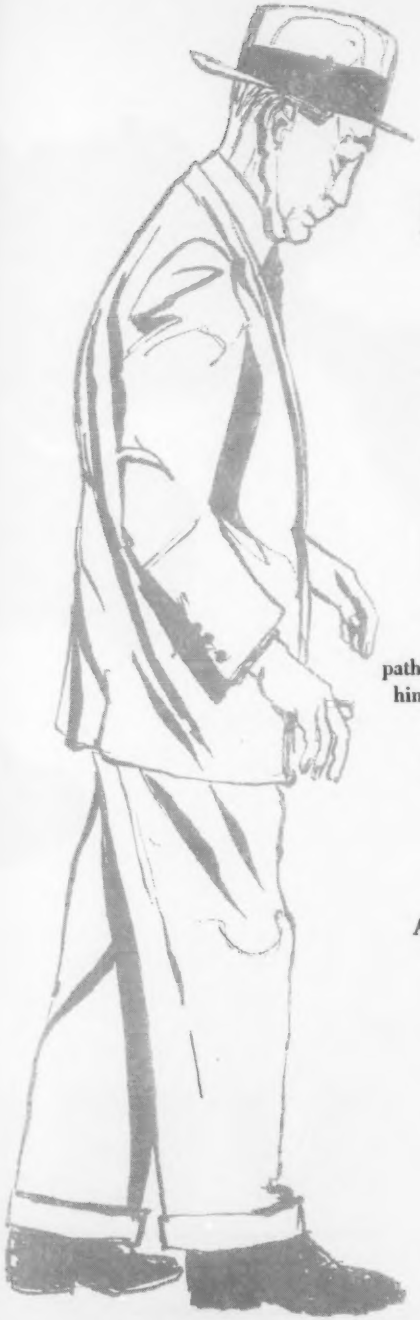
FINE STRUCTURE OF THE NERVOUS SYSTEM—April 23, 1958. Dr. William F. Windle. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

ENROLLMENT FOR ALL COURSES IS LIMITED
Priority will be determined by date of application
No application will be accepted after April 1, 1958

•

Outline of each course, application and further information may be obtained from

Mrs. J. C. McKinley, Executive Secretary
3501 East 54th St., Minneapolis 17, Minnesota



Parkinson's disease

PANPARNIT®

hydrochloride

helps patients

to help themselves

Most distressing of all to the parkinsonian patient is his muscular rigidity...a pathologically imposed strait jacket that forces him to depend on others for many of his needs.

PANPARNIT..."the drug of choice" in 62 per cent* of cases...generally affords substantial relief of spasm, restoring the patient's ability to care for himself and boosting his morale. In many instances PANPARNIT also produces gratifying relief of tremor.

A gradually increasing schedule of dosage is recommended for optimal results.

*Schwab, R. S., and Leigh, D., J.A.M.A. *139*:629, 1949.

PANPARNIT® hydrochloride (caramiphen hydrochloride GEIGY). Sugar-coated tablets of 12.5 mg. and 50 mg.

GEIGY

Ardsley, New York

77487

SQUIBB ANNOUNCES A NEW, IMPROVED AGENT FOR BETTER MANAGEMENT OF PSYCHOTIC PATIENTS

- *schizophrenia*
- *manic states*
- *psychoses associated with organic brain disease*

VES

Squibb Trifluopromazine 10-(3-dimethylaminopropyl)-2-(trifluor

SQUIBB Squibb Quality—the Priceless Ingredient

chemically improved

Modification of the phenothiazine structure potentiates beneficial properties . . .
reduces unwanted effects

pharmacologically improved

Enhanced potency with far less sedative effect

clinically improved

Does not oversedate the patient into sleepiness, apathy, lethargy

Drug induced agitation minimal

Active and rapid in controlling manic states, excitement and panic . . .
in modifying the disturbing effects of delusions and hallucinations . . .
in moderating hostile behavior . . .
in facilitating insight

Intractable behavior patterns brought under control . . . patients made accessible to psychotherapy . . .
nursing care reduced . . .
social rehabilitation hastened

Effective dosage levels may be reached without development of side effects

In extensive clinical experience—singularly free from toxicity

Jaundice or liver damage—not observed
Skin eruptions—rare
Photosensitivity—rare
Hyperthermia—rare
Convulsions—not observed

Dosage: Usual initial dose, 25 mg. t.i.d., to be adjusted according to patient response. See literature.

Tablets of 10, 25 and 50 mg.

'Vesprin' is a Squibb trademark

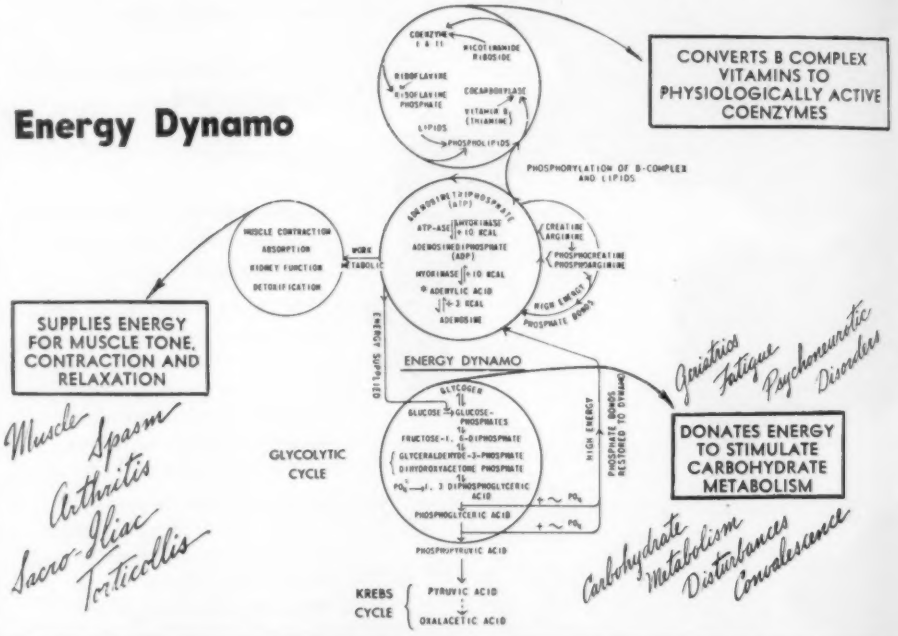
SPRIN

(trifluoro azine hydrochloride

IRONYL®

The Iron Salt of **Adenosine-3-Monophosphate**

THE ROLE OF THE ADENYLIC SYSTEM IN ENERGY EXCHANGES GOVERNING PHYSIOLOGICAL PROCESSES



CLINICALLY: IRONYL, THE IRON SALT OF ADENYLIC ACID, IS AVAILABLE IN ONE CC. AMPULS AND SUBLINGUAL TABLETS.

Gradually the role of the enzyme ADENYLIC ACID in clinical medicine is being clarified, leading to applications in an expanding number of indications, particularly where there are disturbances in the metabolism of muscle energy, and in diseases where there is an early breakdown of nerve or muscle cells.

IRONYL is indicated in the treatment of diseases associated with spasm, insufficient relaxation and lack of muscle tone in striated muscles, in B complex therapy, fatigue and exhaustion.

IRONYL IS SUPPLIED IN BOXES OF 10, 25, 100 AMPULS AND 12, 25, AND 250 TABLETS

PHYSIOLOGICAL CHEMICALS COMPANY, Inc.
New Rochelle, N. Y.

AVAILABLE ON REQUEST an annotated Bibliography, "ABSTRACTS ON THE ADENYLIC NUCLEOTIDES" with particular reference to Yeast Adenylic Acid (Adenosine-3-Monophosphate).

for those with

PARKINSONISM

"... in our experience procyclidine (Kemadrin) proved a worthy addition to the therapy of parkinsonism, because it afforded relief to many patients who had failed to respond to other drugs. It exerts an action against all symptoms of parkinsonism ... hence it may be employed as the basic drug in commencing treatment with new cases."

Zier, A. and Doshay, L. J.: Procyclidine Hydrochloride (Kemadrin) Treatment of Parkinsonism in 108 Patients, Neurology (July) 1957.

"... in our series of 30 severe Parkinsonism sufferers, 21 obtained moderate to good relief with the use of this new agent, Kemadrin, in combination with other drugs."

Lerner, P. F.: Kemadrin, a New Drug for Treatment of Parkinsonian Disease, J. Nerv. & Ment. Dis. **123**:79 (Jan.) 1956.

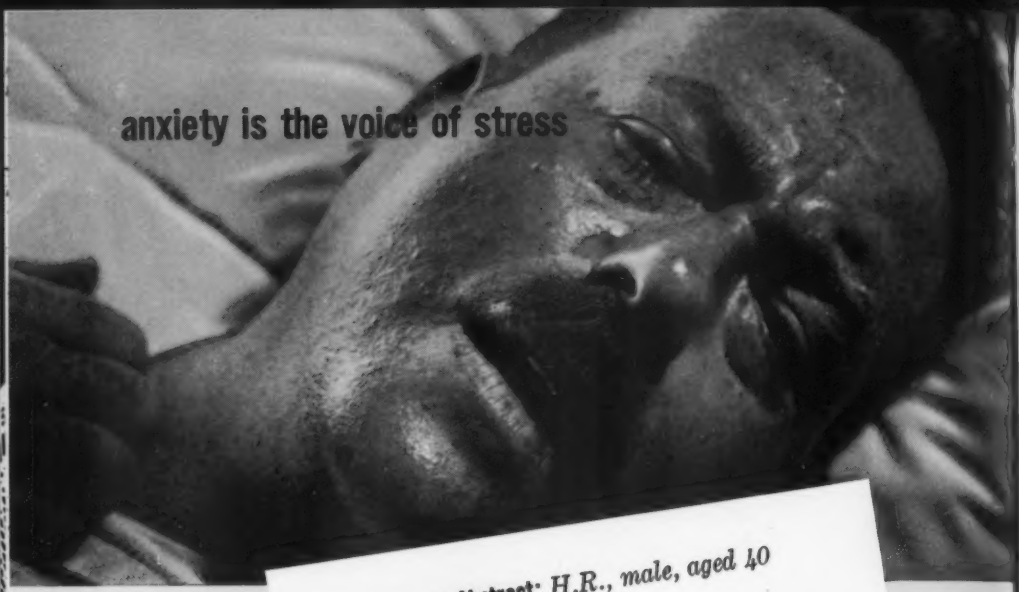
Smoother activity,
and *brighter expression*

with 'KEMADRIN'®

Also indicated for the treatment of drug-induced symptoms resembling parkinsonism, developing during treatment of mental patients.

'KEMADRIN' brand Procyclidine Hydrochloride
Tablets of 5 mg., scored. Bottles of 100 and 1,000.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.



Case-Report Abstract: *H.R., male, aged 40*

Severe anxiety complicating acute posterior myocardial infarction, with sinus tachycardia and premature ventricular contractions. Prompt improvement followed the use of EQUANIL to calm the patient. The heart rate slowed, the premature contractions subsided, and the patient responded to reassurance. Medication with EQUANIL continues, and the patient has returned to work.[1]

"Cardiac patients who show significant manifestations of anxiety should receive ataractic treatment as part of the therapeutic approach. . . ."[1]

1. Waldman, S., and Pelner, L.: Am. Pract. & Digest Treat. 8:1075 (July) 1957.

heart disease is a state of stress

EQUANIL
Meprobamate
PHENERGAN® HCl
Promethazine HCl
SPARINE® HCl
Promazine HCl

A Wyeth normotropic drug for nearly every patient under stress

Wyeth®
Philadelphia 1, Pa.

Equanil®
Meprobamate

Relieves tension—mental and muscular

Neurology Volume 8 • Number 2

Arteriovenous Anomalies of the Brain

A Review and Presentation of 37 Cases

Frank M. Anderson, M.D. and Marvin A. Korbin, M.D.

ARTERIOVENOUS MALFORMATIONS of the brain are challenging lesions which have become more frequently recognized as a cause of certain serious neurologic symptoms demanding accurate diagnosis and carefully planned therapy. Purpose of this paper is to review the characteristics of these anomalies, appraising the experiences of others and ourselves in coping with the diagnostic and therapeutic problems involved.

PATHOLOGY AND CLASSIFICATION

Classification of cerebral vascular neoplasms and malformations has been complicated by uncertainties regarding the origin and exact nature of many of these lesions, leading to complex terminology of limited clinical value.[1-3] This presentation does not have reference to neurocutaneous angiomatosis (Sturge-Weber syndrome) or to true tumors such as angioblastoma or angioblastic meningioma, but is concerned with the congenital non-neoplastic vascular abnormality known as arteriovenous anomaly, arteriovenous malformation, or angioma, comprising essentially a coiled mass of arteries and veins partially separated by thin strips of sclerotic nervous tissue and lying within a bed formed more by displacement than invasion of the surrounding cerebrum or cerebellum. Differentiation of these anomalies into "arterial" or "venous" is difficult or impossible in the usual case and has no practical bearing on the method of treatment.

In addition to the gross malformations, very small or microscopic anomalies of similar fundamental nature have been identified. These are known as "cryptic" arteriovenous hamartoma[4] or small angiomatous malformations and are composed of a tiny clump of structurally defective arteries and veins lying within the brain substance or in the depths of a sulcus (figure 1A). These clinically important lesions should be distinguished from collections of dilated capillaries known as telangiectases, which are occasionally found incidentally at autopsy and occur most commonly in the pons (figure 1B). Unlike the small angiomas, telangiectases do not ordinarily rupture and probably have no clinical significance.

Arteriovenous anomalies range upward in size to huge masses occupying a major portion of a cerebral or (much less frequently) cerebellar hemisphere and extend inward in a roughly cone shape, often reaching from cerebral cortex to ventricle; multiple lesions are found occasionally (figure 2). The vessels are of variable caliber and capillary connections between arteries and veins may be absent, these vessels anastomosing directly; microscopically the arteries are seen to be hypertrophic, with scattered mural calcifications. When a lesion of this type is viewed at operation, it is obvious that blood is being conveyed directly from arteries to veins, causing pink coloration and distention of the latter vessels, through whose thin walls blood can be seen swirling. Appearance of the anomaly may be formidable indeed, particularly if the brain is tense with edema.

From the department of surgery (neurological), University of Southern California School of Medicine, and the service of neurological surgery, Los Angeles County Hospital, Los Angeles, California.

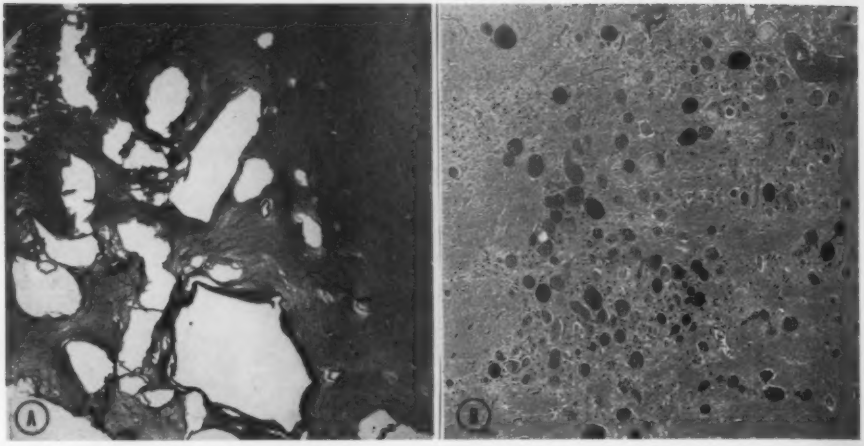


FIG. 1. *A.* Low power photomicrograph of "cryptic" arteriovenous anomaly in temporal lobe of autopsy specimen. This caused no symptoms during life, as is characteristic of such lesions unless rupture occurs. *B.* Telangiectasis in the pons. Unlike the minute arteriovenous malformations, telangiectases do not often rupture and usually are incidental autopsy findings. Hematoxylin and eosin stains.

Most commonly, angiomas are supplied by enlarged branches of the middle cerebral artery and the distended draining veins enter the superior sagittal or lateral sinus, but many variations exist. Major blood supply may be from the anterior or posterior cerebral arteries or various combinations of anterior, middle, and posterior cerebrals of one or both sides and drainage is occasionally diverted, principally into the veins of Galen. Anomalies in the brainstem and cerebellum are fed by branches of the vertebral-basilar system, perhaps with additional vessels from the posterior cerebral artery. If external carotid branches also contribute, the scalp, skull, and meninges, as well as the cerebrum, become involved in the vascular process and surgical eradication of the lesion is rendered difficult and hazardous.

Arteries other than those supplying the vascular mass are often poorly filled at angiography, indicating that the large arteries and wide venous connections of the malformation draw an abnormal volume of blood from one or both sides and possibly reduce circulation in other parts of the brain to a critical minimum (figure 3).

SYMPTOMATOLOGY

Vascular anomalies of the brain tend to make themselves manifest in the age group between 10 and 30 years, although cases have been noted in infancy and old age; they are apparently somewhat commoner in males than females. While about 90 per cent are discovered before the age of 40,[5] even a sizeable lesion may never cause symptoms and may be found incidentally at autopsy in the brain of an elderly individual who died of unrelated causes. Many writers have noted epilepsy as the commonest initial symptom of supratentorial anomaly, but incidence varies widely, ranging from 26 per cent of patients[6] to 62 per cent.[5] Convulsions were the first complaint in only 24 per cent of our patients (nine cases). Seizures may occur over periods of many years and do not necessarily increase in frequency or severity; they tend to be focal or lateralized but are not infrequently generalized, and often respond well to anticonvulsant drugs.

Hemorrhage is the first symptom in a high proportion of patients with intracranial vascular anomaly[6–9] (our series 54 per cent). Onset is usually precipitous, blood issuing from a structurally weak vessel and pouring quickly into the ventricular system or forcing into cerebral substance or subarachnoid space. The sudden cerebral compression and abrupt rise in intracranial pressure produce headache, stupor, vomiting, convulsions, or hemiparesis, depending on rate and situation of the hemorrhage. If the initial attack is not fatal, hemorrhage may recur; it is not unusual for patients to describe several episodes of bleeding many months or years apart before diagnosis is established.

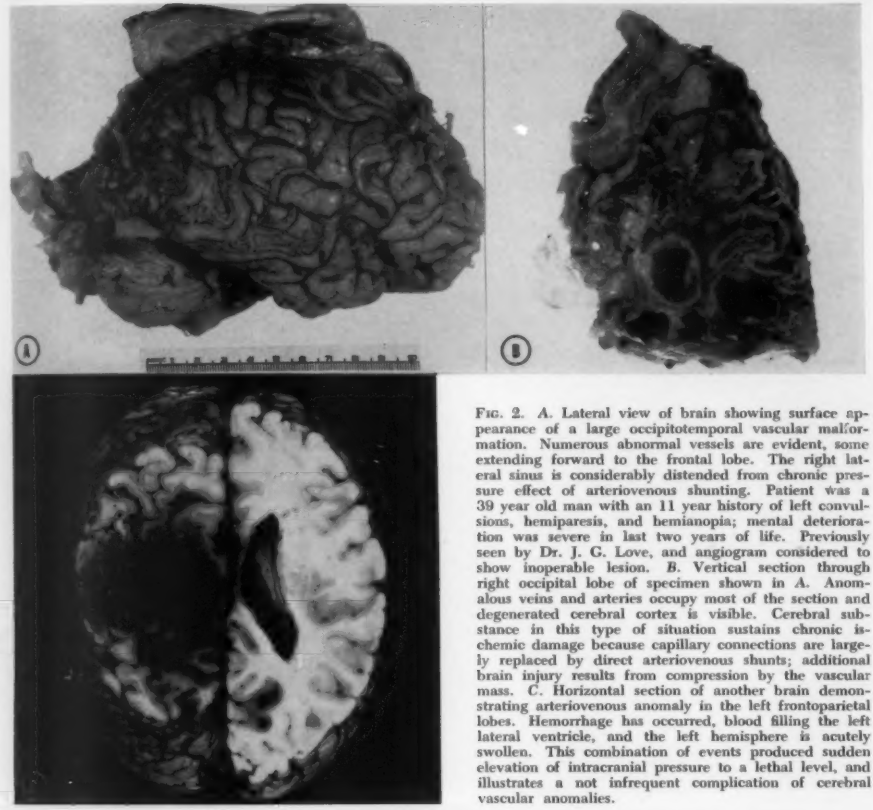


FIG. 2. *A.* Lateral view of brain showing surface appearance of a large occipitotemporal vascular malformation. Numerous abnormal vessels are evident, some extending forward to the frontal lobe. The right lateral sinus is considerably distended from chronic pressure effect of arteriovenous shunting. Patient was a 39 year old man with an 11 year history of left convulsions, hemiparesis, and hemianopia; mental deterioration was severe in last two years of life. Previously seen by Dr. J. G. Love, and angiogram considered to show inoperable lesion. *B.* Vertical section through right occipital lobe of specimen shown in *A.* Anomalous veins and arteries occupy most of the section and degenerated cerebral cortex is visible. Cerebral substance in this type of situation sustains chronic ischemic damage because capillary connections are largely replaced by direct arteriovenous shunts; additional brain injury results from compression by the vascular mass. *C.* Horizontal section of another brain demonstrating arteriovenous anomaly in the left frontoparietal lobes. Hemorrhage has occurred, blood filling the left lateral ventricle, and the left hemisphere is acutely swollen. This combination of events produced sudden elevation of intracranial pressure to a lethal level, and illustrates a not infrequent complication of cerebral vascular anomalies.

Chronic headache is a less common presenting symptom and has been described as generalized and gradually increasing by most writers, though McKissock[10] and also MacKenzie[11] noted that head pain was often unilateral, confined to the side of the anomaly, and of migrainous character. On the other hand, Walker[5] believed headache in patients with vascular anomaly was no more common than in the general population.

Regardless of which may appear first, a high proportion of patients with supratentorial arteriovenous anomaly experience convulsions, intracranial bleeding, headache, or hemiparesis at some time and, in addition, are afflicted with less frequent symptoms, including mental deterioration and a variety of local neurologic defects from direct encroachment or pressure by the lesion. Mental disturbance, due to hypoxic effect of arteriovenous shunting or cerebral injury from hemorrhage and obstructive hydrocephalus, ranges from mild to severe and has been reported as present in 50 per cent of cases[12] to 2 per cent or less.[5,11,13] Frequency of significant mental defect recorded in several reports[5,6,8,9,11–13] and in our material averages 14 per cent. Visual field defects are occasionally described when the abnormality bears on some portion of the optic radiation, and diplopia may be caused by sixth nerve paralysis secondary to raised intracranial pressure. A few patients are aware of head noise which may or may not be audible as a bruit to the examiner.

The "cryptic" variety of arteriovenous malformation is reported most commonly in children and young adults, suggesting that this type tends to rupture early in life. A minute anomaly may not be visualized in an arteriogram (figure 4) and will be clinically silent

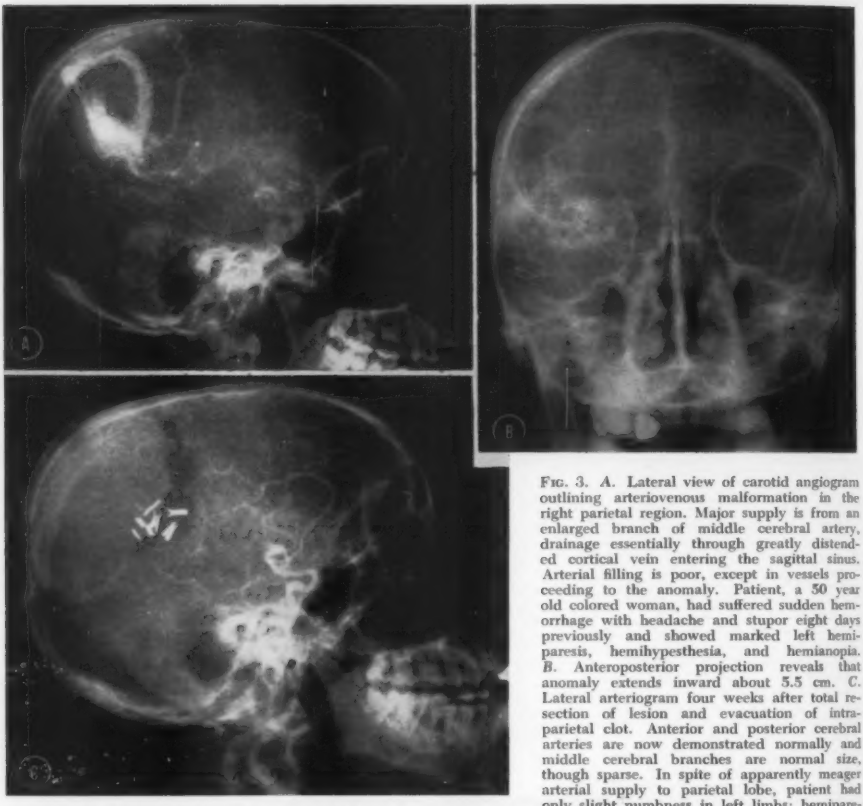


FIG. 3. *A*. Lateral view of carotid angiogram outlining arteriovenous malformation in the right parietal region. Major supply is from an enlarged branch of middle cerebral artery, drainage essentially through greatly distended cortical vein entering the sagittal sinus. Arterial filling is poor, except in vessels proceeding to the anomaly. Patient, a 50 year old colored woman, had suffered sudden hemorrhage with headache and stupor eight days previously and showed marked left hemiparesis, hemihypesthesia, and hemianopia. *B*. Anteroposterior projection reveals that anomaly extends inward about 5.5 cm. *C*. Lateral arteriogram four weeks after total resection of lesion and evacuation of intraparietal clot. Anterior and posterior cerebral arteries are now demonstrated normally and middle cerebral branches are normal size, though sparse. In spite of apparently meager arterial supply to parietal lobe, patient had only slight numbness in left limbs; hemiparesis was mild; visual field improved. Patient had one convulsion nine months later, and has taken anticonvulsant drugs since with no further seizures (two years). Well defined improvement in pattern of cerebral circulation can almost invariably be demonstrated angiographically after resection of an arteriovenous malformation.

unless rupture occurs, in which event sudden release of blood into the cerebrum or subarachnoid spaces causes acute increase in intracranial pressure, headache, stupor, and other symptoms identical to those produced by hemorrhage from large vascular anomalies or aneurysms. Bleeding is often progressive and there is a high fatality rate. Hemorrhage may destroy the anomaly, leaving in the postmortem brain only unexplained intracerebral clot, a lesion often tenuously ascribed to trauma and classified as posttraumatic hemorrhage. Several writers[1,4,7,14] have stressed that the wall of a hemorrhagic cavity must be carefully fixed and examined microscopically if a minute vascular anomaly is to be recognized as the true source of bleeding.

An interesting and unusual malformation is that comprising direct arteriovenous shunt between certain cerebral arteries and the veins of Galen.[15,16] It is formed by branches of anterior, middle, or posterior cerebral arteries anastomosing with internal cerebral veins, causing in some instances huge distention of the great vein of Galen, which in turn compresses the Sylvian aqueduct and produces internal hydrocephalus. The lesion may rupture, giving rise to the usual symptoms of intracranial hemorrhage, but in infants and young children especially, chronic aqueductal occlusion causes "pressure" symptoms, enlargement of the head, and other difficulties superficially indistinguishable from congenital hydrocephalus.[17]

Unlike many of the supratentorial anomalies, similar lesions in the cerebellum usually cause no characteristic symptom complex, although spontaneous intracerebellar and subarachnoid hemorrhage may occur from such a lesion, precipitating acute cerebellar symptoms and sudden elevation of intracranial pressure. If the mass does not bleed, a chronic and variable complex of headache, ataxia, vomiting, and diplopia may result and be erroneously ascribed to multiple sclerosis or neoplasm of the cerebellum.[6,18]

Progressive stupor, convulsions, and other symptoms of intracranial hypertension after bleeding from an arteriovenous abnormality are sometimes considerably augmented by accumulation of blood in the subdural space with formation of subdural hematoma, and this complication may demand early drainage as a life-saving measure. It has been suggested[19] that slow or repeated mild bleeding from an unsuspected and otherwise asymptomatic vascular anomaly accounts for subdural hematoma in a certain proportion of the patients who are found to have this rather common lesion. An opposite type of complication, namely thrombosis of large vessels within the angioma, is probably unusual and offers little chance of ameliorating symptoms by reducing the size or potential hazardousness of the lesion, although occasionally such a fortunate sequence may occur.[20] However, occlusion of a large artery (or vein) by thrombus may cause sudden increase in neurologic deficit with hemiplegia, hemianopia, and the like, an event presumed to have occurred in one of our patients when weakness in a previously paretic leg abruptly increased, unaccompanied by headache or other symptoms of cerebral hemorrhage.

Complaints attributable to intracranial vascular malformations often (but not invariably) increase in severity with the passage of years, even though no bleeding occurs. Chronic cerebral hypoxia is a logical explanation for such progression, but in addition it has been assumed that the lesion gradually enlarges due to continuing distention of veins by blood under arterial pressure, thereby increasing compressive forces exerted by the mass on the brain.[6,8,11,12,21] Olivecrona and Riives[12] described one patient in whom they felt enlargement of the lesion was shown, and Potter[9] presented angiographic evidence of growth of a small angioma in a seven-week period, a process which he felt took place by rupture of small shunting vessels, formation of false aneurysm, then repetition of this cycle. Paucity of reported objective data suggests that, while enlargement may well occur in the early years of life, growth in the adult is perhaps unusual or slight in most cases.

FIG. 4. Anteroposterior carotid arteriogram delineating a small arteriovenous anomaly of the same general order as that shown in figure 1A. Other projections showed this angioma to be in parieto-occipital region. Patient was 19 years old and entered hospital shortly after intracerebral hemorrhage, which resulted in severe headache, left hemiparesis, and hemianopia. Spinal fluid was bloody. No operation was permitted and slow recovery followed, headache persisting for several weeks. Patient now asymptomatic (four years).

Definite evidence of increase in size of arteriovenous anomaly was provided in one of our cases. This patient had an arteriogram for investigation of intracranial hemorrhage in 1951, when 19 years old. A large left temporal vascular lesion was demonstrated but considered inoperable and no surgical therapy was advised. Convulsions began 18 months later, continuing without other noteworthy symptoms, and periodic skull films showed increasing density in a small calcification within the angioma. Five years later a second hemorrhage occurred and arteriography was repeated. This study revealed conclusively that enlargement of the vascular lesion had occurred (figure 5). Surgical exploration was performed elsewhere but the mass was not removed and the patient has recently recovered from a third subarachnoid hemorrhage.

PHYSICAL FINDINGS AND DIAGNOSIS

Arteriovenous anomaly of the brain should be suspected in a patient who has had epilep-

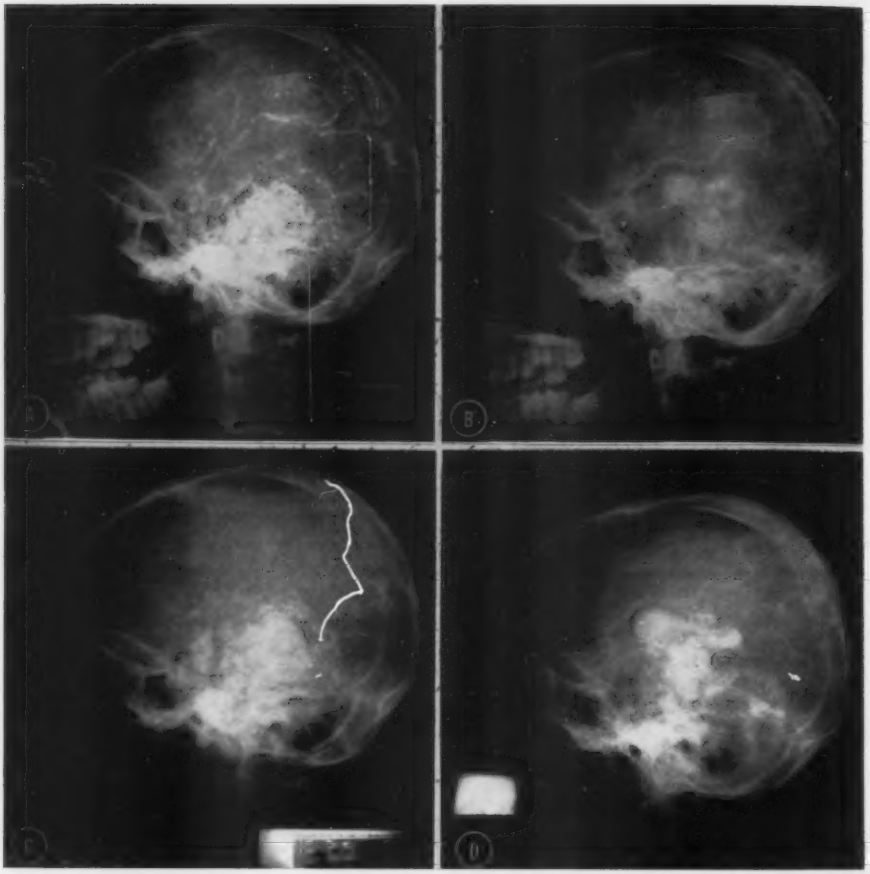


FIG. 5. *A*, arterial, and *B*, venous phase of carotid arteriogram in 19 year old male, showing large anomaly in left (major) temporal lobe, considered inoperable. Patient had been entirely well until signs of hemorrhage occurred: headache, stupor, meningismus, and bloody spinal fluid, for which arteriogram was done. Patient recovered except for occasional convulsions until five years later when the lesion again bled. *C*, arterial, and *D*, venous phase in arteriogram performed five years after the above study. Careful review of all films demonstrated definite enlargement of the anomaly in arterial as well as venous components. Exploration was done elsewhere, but the lesion was not attacked; patient subsequently had a third hemorrhage (seven months ago) and recovered.

tic seizures and one or more episodes of intracranial hemorrhage. Probability of such a lesion is increased if seizures are focal or lateralized, and it has been stated[21] that the presence of cranial bruit in such a patient almost assures the diagnosis. If no recent hemorrhage has occurred, neurologic examination may be entirely negative and spinal fluid probably normal, but careful testing may elicit such focal signs as a visual field defect, slight weakness or numbness of one side, disparity in deep or superficial reflexes, or a Babinski sign. The occasional case will present papilledema and other evidences of intracranial hypertension caused by a large or strategically located vascular malformation, thereby simulating cerebral neoplasm.

In a patient whose lesion has bled recently, hemiparesis is common and hemihypesthesia probably fairly frequent but less apparent and easily overlooked; hemianopia, detectable if the patient is reasonably alert, is usually pres-

ent when intracerebral hemorrhage involves the temporal or occipital lobe. Often noted are convulsive movements, fever, stiff neck, stupor, and confusion, due to raised intracranial pressure, as well as meningismus from blood. Spinal fluid is usually under increased pressure and bloody or xanthochromic but, if hemorrhage is confined to the cerebral substance and does not enter the subarachnoid space or ventricle, fluid is clear and may remain so. Reaction of meninges in the basilar cisterns to blood occasionally causes occlusion of spinal fluid pathways two weeks or more after bleeding, and chronic intracranial hypertension as well as internal hydrocephalus then supervene.[22]

Careful auscultation of the head and eyes should be included in routine neurologic examination, since detection of bruit by this simple method will quickly suggest the possibility of intracranial vascular anomaly. However, bruit is audible over some vascular neoplasms, in patients with carotid-cavernous fistula, and in a certain proportion of normal infants and young children.[23,24] We and others[25] have noted a definite systolic bruit in a few patients with small saccular carotid aneurysm, and it has been shown that bruit may be detectable contralateral to thrombosed cervical carotid artery.[26] Objective head noise due to arteriovenous malformation depends upon several factors besides location of the lesion; though a large cortical mass may not produce bruit, incidence is high with larger lesions, particularly those which involve the cranial bone or scalp. Frequency of bruit varies in reported series from 15 per cent[6] to 50 per cent,[11] averaging 22 per cent, and in our material was noted in six of the 20 patients (30 per cent) in whom auscultation was recorded.

Electroencephalography in patients with vascular anomaly has not been found by others to be of reliable diagnostic value, and in the present series indicated the site of the lesion in only four of 15 patients tested before and after rupture. It appears that the electroencephalogram does not assist in differential diagnosis of vascular malformations, though it may offer help with localization or lateralization before arteriography is performed.

Plain skull films showed curved lines of calcification in a small portion of the lesion in four of our cases, erosion of bone adjacent to the anomaly in two, a circular opening for passage of a large emissary vein in another, and marked enlargement of meningeal grooves in an eighth case. Changes of this sort, observed in 22 per cent of our patients, are apparently to be expected in a definite proportion of such cases, though vessel calcification and bone erosion increase gradually with passage of time and incidence will vary with age of the patient and location of the anomaly. Others have reported similar findings, and it is worth stressing that plain skull films should be scrutinized very carefully when vascular anomaly is even remotely considered. Pneumoencephalogram or ventriculogram may reveal changes indicative of vascular malformation, but findings other than possible ventricular enlargement are apt to be slight and overlooked or disregarded. Evidence of space-taking lesion in the cerebrum, together with focal cortical atrophy or irregular indentations in a ventricle, has been reported as diagnostic;[12,27] the latter was noted in one of the three patients in our series who underwent pneumoencephalography.

FIG. 6. Small left parietal malformation in 28 year old man with history of intracranial hemorrhage on three occasions since age 24. Recent memory was somewhat defective and there was mild anomia. This arteriogram shows enlargement and straightening of middle cerebral branches supplying the anomaly, other arteries being small or unfilled. At operation, no surface abnormality was encountered and resection was decided against. Patient recovered but fatal hemorrhage occured 18 months later.

The most important diagnostic test for persons suspected of having arteriovenous anomaly is cerebral arteriography in anteroposterior and lateral projections, preferably with a serial roentgenogram device. Risk of this procedure is low and, if patient's condition is reasonably satisfactory, arteriography should be performed within a day or two after hemorrhage has occurred. Bilateral common carotid injections with 35 per cent Diodrast, 50 per cent Hypaque (sodium diacetrizoate), or similar media will suffice if anomaly is seen to fill from an-

terior or middle cerebral arteries, but if there is abnormality of the posterior cerebral circulation, vertebral arteriography may be required in addition; the latter study is advisable also in a patient whose history indicates probability of a vascular lesion but in whom no abnormality of carotid system is demonstrated.

In appraising the films for consideration of surgical therapy, it is essential to determine which arteries are principal contributors to the anomaly and to decide whether it is irrigated by one or both carotids or from vertebral as well as carotid circulation. Size at the moment of maximum filling, avenues of venous drainage, and precise relation of abnormal vessels to important areas of the brain must be noted carefully. Presence of intracerebral hematoma is suggested by a "blank" area near the lesion, with displacement of adjacent vessels. A filling defect alone indicates the possibility of clot secondary to rupture of a minute angioma or unfilled saccular aneurysm, a picture sometimes indistinguishable from that caused by cerebral abscess or avascular neoplasm. At the

TABLE 1

LOCATION OF LESION, AUTHOR'S CASES	
Parietal	12
Frontal or frontoparietal	7
Temporal or temporo-occipital	7
Parieto-occipital	6
Occipital	3
Midline (ant. cerebral—vein of Galen)	2
Cerebellar	0
	37

PRINCIPAL OR EXCLUSIVE ARTERIAL SUPPLY	
Middle cerebral artery	23
Anterior cerebral	7
Posterior cerebral	6
External carotid branches	1
	37

Vertebral arteriography was performed in only 3 cases. Possibly injection by this route would have shown major supply via posterior cerebral arteries in many of the posteriorly situated lesions.

TABLE 2

SUMMARY OF SYMPTOMS

Initial Symptoms:			*Patients*
Hemorrhage			20
Convulsions			9
Lateralized or focal, 7; generalized, 2			
Headache (chronic)			5
Pain in face			2
Prominent facial veins (child)			1
Total			37

Symptoms and Signs Noted in Course of Illness:			*Patients*
Hemorrhage			27*
Convulsions			18
Acute, with hemorrhage	5		
Chronic	13		
Focal or lateralized		10	
Generalized		8	
Headache (not due to acute hemorrhage)			7
Mental deterioration			3
Objective cranial bruit			6†
Hemiparesis			13
Acute, with hemorrhage	12		
Chronic, no hemorrhage	1		
Monoparesis, chronic, worse postictal			2
Hemianopia following hemorrhage			6

*(42 total hemorrhages)
†(in 20 patients)

TABLE 3

TREATMENT AND RESULTS IN 37 PATIENTS

Intracranial Operation			
Total removal lesion			9
Normal postoperatively	4		
Hemianopia*	2		
Hemiparesis (seizures relieved)	1		
Preexisting hemiparesis lessened, aphasia now absent	1		
Operative death	1		
Ligation accessible afferent arteries			3
Improved	1		
Unchanged	1		
Subsequent minor hemorrhage	1		
Exploration only			4
Unchanged, fair	2		
Died of subsequent hemorrhage months later (Fig. 6)	2		
Drainage intracerebral hemorrhage only (Later had progressive mental deterioration)			1
Total			17

*One of these is recent case of Dr. F. L. Johnson, and permanent status not yet determined.

Ligation Extracranial Arteries			
Resection abnormal carotid bifurcation in neck (Lesion later removed; no neurologic deficit)			1
Ligation (elsewhere) meningeal and scalp arteries, right carotid in neck (Facial pain relieved: died 3 yrs. later [Fig. 2])			1
Ligation 1 carotid in neck (Improved 2 months. Unable to trace)			1
Total			3
No Operation Performed			
Unchanged			7
Follow-up 6 months to 18 years. Facial pain, seizures, persisted when present.			
Improved			4
Headache regressed in two. Seizures less frequent in two.			
Untraceable, or follow-up interval too short			3
Known dead			2
Total			16

Radiation Therapy, 5 patients
(some with subsequent surgery)

1. Facial pain unchanged by therapy. Mental deterioration and seizures progressed.
2. Head and face pain continued. No other symptoms.
3. Had subsequent hemorrhage, recovered; now asymptomatic (3 years).
4. Headache improved. Four years later had third hemorrhage; died after operation.
5. Remains normal 7 years after single hemorrhage.

opposite extreme, differentiation is occasionally difficult between a well-demarcated arteriovenous anomaly and a highly vascular tumor such as angioblastic meningioma.

TREATMENT

Because of many variables in size and location of the lesion, prominence of symptoms, and status of the patient and also because of variations in the surgeon's experience and inclinations, we strongly believe it unwise to imply that any single method of treatment is appropriate for cerebral arteriovenous anomalies.

Therapy may be considered under two general headings: expectant and surgical. Each case must be appraised carefully and qualifying circumstances recognized, but expectant or nonsurgical treatment is usually advised if the lesion is 1) large, deep, and supplied by main trunk of the middle cerebral artery (removal of such lesion would necessitate sacrifice of the artery with resultant hemiplegia and perhaps aphasia), 2) bilateral or directly fed by branches of both carotid arteries (an anomaly of this nature is usually very large and may occupy a considerable part of one hemisphere), or 3) within or closely applied to the brainstem. Treatment of these three general types of lesions is confined to administration of appropriate anticonvulsant drugs, sedatives, and analgesics, unless rupture has occurred. X-radiation has been concluded by most writers to have limited therapeutic value, and in five of our cases so treated the results were unimpressive (table 3); recently, however, Potter[9] has urged reconsideration of this method.

In the event of hemorrhage, supportive measures are necessary to combat the often severe effects of sudden rise in intracranial pressure and consequent cerebral ischemia and edema; oxygen is given, fluid and electrolyte balances carefully maintained, and blood transfusion provided as indicated. Intravenous hypertonic sucrose, and urea solutions[30] are employed for their possible value in diminishing cerebral edema. When the arteriogram shows an inoperable vascular anomaly but delineates a large intracerebral clot or subdural hematoma, surgical drainage may on occasion be justified for relief of focal or pressure symptoms, if general condition of the patient permits and cerebral function is judged not to be irretrievably compromised.

Surgery is not advised in persons of advanced age or with marked mental deterioration or severe chronic debility, even though the lesion shown angiographically may be accessible and presumably not unduly difficult to remove; conservative approach is recommended in these circumstances because the risks of operation would in all probability outweigh the chances of useful long-term gain.

Surgical procedures used in treatment of cerebral vascular anomalies include: 1) total removal; 2) exposure of the lesion, ligation of afferent arteries, and electrocauterization of accessible portions with "cutting" current (these two methods are elaborated upon below); 3) closure of feeding arteries intracranially by clips or ligatures without disturbing other parts,[8,28] a technic of value when supply is exclusively from one or two approachable arteries and the lesion itself unfavorably situated; 4) ligature of one or more extracranial arteries, such as the internal carotid in the neck plus one or both external carotids, a method generally felt to be of questionable value (Olivecrona and Riives[12] reported hemiplegia in four of six patients treated by internal carotid ligation and considered this approach more hazardous than excision of the anomaly); 5) removal of subdural or intracerebral hematoma with or without further procedure. Such collections of blood should always be evacuated when craniotomy is done and in critically ill patients may demand immediate drainage.[19,28] If angiogram has indicated intracerebral hematoma but failed to define its source, the hemorrhagic cavity should be carefully searched for small arteriovenous anomaly or aneurysm.

Complete excision of the lesion is considered to be the ideal treatment whenever technically feasible, if symptoms are progressive or of severe nature, and particularly if there have been one or more episodes of intracranial hemorrhage.[6,8,12,20,21,27,29] The less radical method of intracranial occlusion of feeding arteries, perhaps combined with cauterization of accessible anomalous vessels, is utilized when removal is impossible without sacrifice of important cerebral areas. In defense of direct surgical attack on the lesion, two of our cases may be cited wherein treatment was too conservative. Both were young males in whom arteriography revealed anomaly about 3 cm. in maximum extent, one being parietal (figure 6), the other posterior frontal. Hemorrhage had occurred three times in one patient, once in the other. Although angiographically the masses appeared superficial, operation in each instance showed no abnormality on the cortex and no dissection or ligation was done, the operator

concluding that the concealed lesion was better left undisturbed. The patients recovered fully after surgery, but each had a subsequent hemorrhage (six and 18 months postoperatively) which was quickly fatal.

Surgical preparations and technic of intracranial operation for arteriovenous malformation have been described adequately by several authors and will not be given in detail here. It is desirable that the patient be maintained in a hypothermic state by a skilled anesthetist who may administer Arfonad or other hypotensive agents judiciously as indicated. Of great advantage is placement of loose tapes about the carotid arteries and perhaps the vertebrals as well, permitting an assistant to close these vessels temporarily if troublesome bleeding is encountered. Blood for transfusion must be at hand in sufficient amount to replace any sudden, severe hemorrhage and two large caliber intravenous needles should be in place before operation is begun.

The bone flap must be accurately located to give best access to arterial supply of the malformation and spinal drainage utilized when needed to slacken the brain before the dura mater is opened. Subdural or intracerebral clots are then evacuated as fully as possible. If anomaly presents on the surface all superficial arterial feeders should be closed with clips and divided, after which dissection is carried inward close to the vascular mass and arteries secured as encountered; a subsurface anomaly is revealed by careful incision of the cortex and overlying white substance. As dissection proceeds, the lesion shrinks and can be partially retracted outward while its draining veins are ligated or clipped, permitting removal. If anomaly is found to be too extensive or critically situated, the best course may be to remove as much as possible and desiccate accessible remaining portions with low cutting current of the electrocautery, avoiding heroic attempts at total removal. As a final measure, blood pressure should be restored to normotensive level and the operative field minutely checked for bleeding points. Hemostasis is absolutely essential before the dura is closed and bone flap replaced.

Postoperative maintenance includes very close observation of the patient's neurologic status and vital signs to detect evidence of intracranial hemorrhage or serious brain edema as early as possible. Carbogen inhalations and intramuscular papaverine are probably useful to counteract vascular spasm and improve cerebral circulation. Deepening stupor, lateralized or general convulsions, and progressive weakness of limbs may be due to bleeding or cerebral edema and differentiation is apt to be difficult, but if intravenous urea solution[30] gives no improvement, exploration of the wound for hemorrhage is usually indicated. In one of our patients hemorrhage developed on the first postoperative day and, although it was evacuated without undue delay, hemiparesis and mild aphasia persisted, probably because of brain damage from compression. Ideally, aftercare might include maintenance of the patient in a hypothermic state for 24 hours or more, but this requires rather elaborate equipment and trained personnel not generally available.

RESULTS

Operations for cerebral arteriovenous malformation have given favorable results in the majority of reported cases. A representative series is that of Olivecrona and Riives,[12] who carried out complete excision in 24 patients, with three deaths due to surgical hemorrhage, postoperative clot, and meningitis. Of the survivors, eight were normal and another eight continued to show the neurologic defects exhibited before operation; most were able to work but a few were made worse by surgery. Of five postoperative "invalids," four were so classed prior to surgery and the other was well postoperatively until a paralyzing intracerebral hemorrhage occurred five years later.

Intracranial operation was performed in 30 of the 41 cases reported by Gould and coworkers,[6] but a non-resectable lesion was found in ten and recurrent hemorrhage, severe convulsive state, or mental deterioration caused invalidism or death in most of these. In the patients who had definitive surgery (excision in 15, clipping of arteries in five), operative mortality was 15 per cent. Ten survivors were classified as having good result, three fair and one poor, showing no improvement in preoperative mental defect. The authors concluded that prognosis in patients with untreated vascular anomalies was very poor and they recommended surgical eradication of the lesion whenever feasible, concurring fully with the earlier opinions of Olivecrona and Riives.[12] Generally good results and similar conclusions regarding treatment have been described by several others.[10,17,21,27,28,29,31]

Radical removal of the lesion in Norlen's ten cases resulted in no mortality and no morbidity attributable to surgery.[20] Seven of these patients were restored to normal, one was much improved, and in two patients preopera-

tive neurologic defects persisted but they were less severe. Arteriograms were presented to show that poor filling of normal arteries consequent to shunting of dye through the anomaly was corrected after surgery, postoperative angiograms demonstrating the now well-established fact that excision of the lesion permits symmetric filling of all vessels and definite enlargement of previously small arterial branches (figure 3). This restoration of cerebral circulation to normal may prevent mental deterioration in some patients and perhaps is of prophylactic value against convulsions in persons who do not have seizures prior to surgery. It is very difficult, of course, to substantiate these theories, but mental function in one of Norlen's patients was reportedly improved some months after operation.

Our results are summarized in table 3. Of nine patients in whom resection was carried out, seven were substantially improved, one became hemiparetic but was relieved of severe seizures thus far (18 months), and one operated upon shortly after a third intracerebral hemorrhage died within 24 hours. Intracranial arterial ligature appeared to benefit one patient by reducing headache and convulsions and had no effect in two others. Another eight patients have been followed less than six months since first examination or have been untraceable, hence no conclusions are yet possible regarding the survivors in this group. Only one of these had surgical therapy (carotid ligation) and two died from effects of initial hemorrhage. Of 17 others whose course has been watched for periods of six months to 18 years, five had exploratory operation only, one underwent ligation of extracranial arteries, and intracerebral clot was aspirated in one; the remainder had no surgical treatment. Of these patients eight are unchanged or improved and their neurologic status is normal or nearly so, whereas two had subsequent fatal hemorrhage, another died in status epilepticus, and six surviving patients have varying degrees of neurologic disabliity or convulsions, augmented by bleeding episodes in two. Our results in the group of 17 not undergoing definitive therapy may be summarized thus: Eight are excellent or good, five fair, one is mentally deteriorated, and three are dead.

In a recent review, Paterson and McKissock[8] reported 110 cases, of whom 36 were treated by total excision and 16 by ligation of accessible cortical feeding arteries plus electrocoagulation. Exploration was carried out in nine but no attack was made on the lesion, and in six patients one carotid artery was ligated. Fifteen were given radiation therapy, with or without surgery of some type, and the remaining patients were essentially untreated. Of patients undergoing excision one died postoperatively and two later (one of these from recurrent hemorrhage); three were incapacitated but 29 were restored to normal occupations though a few had minor neurologic defects. In this group 19 had epilepsy preoperatively; of those followed after surgery about 44 per cent were relieved of seizures. Regarding the 16 patients who were treated by intracranial ligation of afferent arteries and/or electrocoagulation, it was stated none was made worse and six were benefited in that epileptic seizures were controlled or reduced; one had two subsequent minor intracranial hemorrhages. These writers summarized their opinion regarding treatment as follows: "whenever possible total excision of the angioma is the ideal method of treatment. Ligation of cortical feeding vessels seems not to be without value in certain instances."

The effect of surgical eradication of arteriovenous anomalies on the course of convulsive attacks cannot be definitely established from most reported material, including our own, because follow-up is not sufficiently long. Olivecrona and Riives[12] and Norlen,[20] surveying results in their patients, felt that surgery was not likely to cure or ameliorate epilepsy and they recommended that operation not be done primarily for this symptom. While the excellent results of Paterson and McKissock suggest that a certain proportion of patients with convulsions will be improved after operation, other symptoms such as hemorrhage and weakness of extremities are currently much stronger indications for surgery, unless seizures are poorly controlled by medication. It should be noted in this connection that any operation involving incision or traumatization of the cortex carries some risk of initiating subsequent convulsive attacks, an undeniable disadvantage of such surgery.

Results of conservative, non-surgical treatment of intracranial vascular anomalies are felt by most investigators to be poor, and particularly strong opinions in this connection were voiced by Olivecrona and Riives[12] and by Gould and associates.[6] Svien and co-workers,[13] however, believed non-surgical treatment was preferable in most instances and were pessimistic about resection, stating that residual neurologic defects were to be expected in most cases because the majority of anomalies in their

experience were within the field of supply of the middle cerebral artery. Paterson and McKissock[8] also reviewed the course of their unoperated patients and found that progress in these 37 was more favorable than expected. Mental deterioration was uncommon and only three had had fatal hemorrhage at the time of report, leading the authors to conclude that the incidence of crippling hemorrhage from arteriovenous anomalies was considerably less than that occasioned by aneurysm of the circle of Willis. It is of interest that in spite of this opinion – directly opposed to that of several other authors – the writers recommended surgical excision of anomalies in preference to other methods of treatment.

Potter[9] advised conservative management and presented extensive follow-up data on 55 patients supporting this view. However, in 38 patients given "symptomatic" treatment, an unstated number underwent surgical procedures involving ligation of vessels and/or removal of intracerebral clot, and in this mixed group it is impossible to determine what role operations played in the generally favorable outcome. The author felt that death from hemorrhage was not apt to occur later than ten years after onset of symptoms and believed, as did Paterson, that effects of bleeding were generally less damaging than those from aneurysm. He noted long survival with only minor disability in four of ten patients given radiation therapy and concluded there may be merit to this treatment of vascular anomalies whenever excision is not practical, though recognizing the method has been tried and largely abandoned in the past.

DISCUSSION

It is important to stress that wide variations in the natural history of untreated cerebral arteriovenous malformations make comparisons of therapeutic methods and end results difficult. Convulsions may increase in severity and frequency or inexplicably diminish; intractable headache sometimes disappears spontaneously, and mental deterioration, relatively early and progressive in some patients, need not develop, even in presence of a large, rapidly shunting lesion. Hemorrhage may be devastating, absent, or recurrent over a considerable span of years without causing serious neurologic loss.

It is clearly impossible with our present knowledge to be certain of the benefits of radiation therapy on such unpredictable lesions. The value of intracranial arterial ligation or incomplete removal of the anomaly may also be questioned, although these latter methods can be evaluated within limits by postoperative arteriography and would seem to offer certain theoretical gains. Total excision is more hazardous from the standpoints of morbidity and mortality but, with careful study and selection of patients, the risks are low and excellent results are often attainable. If excision is accomplished, the patient obtains relief from one of his most troublesome symptoms, namely, concern about the possibility of recurring intracranial hemorrhage, a factor of no small importance in rehabilitation.

Many of the uncertainties referred to can be resolved by continuing appraisal of the long-term outcome of patients who have been carefully investigated and treated systematically by well-defined technics. In time, such surveys will afford logical conclusions upon which appropriate therapy can be grounded. Thus, as experience increases and technical improvements are developed, therapeutic results should improve and many anomalies of type and location now considered hopeless may be excised with minimum risk, or their deleterious effects controlled by judicious application of non-surgical methods.

CONCLUSIONS

1. The subject of congenital intracranial arteriovenous malformations is reviewed from standpoints of pathology, diagnosis, treatment, and results, and a series of 37 cases is presented.

2. General symptoms and signs of such lesions are hemorrhage, convulsive attacks, weakness of extremities, headache, cranial bruit, and mental deterioration, but course is variable and symptoms may be unobtrusive.

3. Diagnosis can be established precisely only by arteriography of carotid and occasionally vertebral circulations. Appropriate angiographic study should be done promptly when diagnosis is suspected, particularly if hemorrhage has occurred.

4. Complete excision of the vascular anomaly is ideal treatment whenever feasible, but the complex factors of accessibility of the lesion and status of patient must be fully evaluated before any decision regarding surgery is reached. This is particularly important because prognosis without operation is favorable in many instances.

REFERENCES

1. Bagley, C., Jr.: Spontaneous cerebral hemorrhage. Discussion of four types, with surgical considerations. Arch. Neurol. & Psychiat. 27:1133, 1932.
2. Cushing, H., and Bailey, P.: Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Hemangioblastoma. Springfield, Illinois: Charles C Thomas, 1928.
3. Noran, H. H.: Intracranial vascular tumors and malformations. Arch. Path. 39:393, 1945.
4. Russell, D. S.: The pathology of spontaneous intracranial hemorrhage. Proc. Roy. Soc. Med. 47:689, 1954.
5. Walker, A. E.: Clinical localization of intracranial aneurysms and vascular anomalies. Neurology 6:79, 1956.
6. Gould, P. L., Peyton, W. T., and French, L. A.: Arteriovenous malformations of the brain. Bull. Univ. Minn. Hosp. 26:611, 1955.
7. Crawford, J. V., and Russell, D. S.: Cryptic arteriovenous and venous hamartomas of the brain. J. Neurol., Neurosurg. & Psychiat. 19:1, 1956.
8. Paterson, J. H., and McKissock, W.: A clinical survey of intracranial angiomas with special reference to their mode of progression and surgical treatment: A report of 110 cases. Brain 79:233, 1956.
9. Potter, J. M.: Angiomatous malformations of the brain: Their nature and prognosis. Ann. Roy. Coll. Surgeons England 16:227, 1955.
10. McKissock, W.: Intracranial angiomata. Ann. Roy. Coll. Surgeons England 7:472, 1950.
11. MacKenzie, I.: The clinical presentation of the cerebral angioma; A review of fifty cases. Brain 76: 184, 1953.
12. Olivecrona, H., and Riives, J.: Arteriovenous aneurysms of the brain. Their diagnosis and treatment. Arch. Neurol. & Psychiat. 59:567, 1948.
13. Svien, H. J., Olive, I., and Angulo-Rivero, P.: The fate of patients who have cerebral arteriovenous anomalies without definitive surgical treatments. J. Neurosurg. 13:381, 1956.
14. Margolis, G., Odom, G. L., Woodhall, B., and Bloor, B. M.: The role of small angiomatous malformations in the production of intracerebral hematomas. J. Neurosurg. 8:564, 1951.
15. Jaeger, J. R., Forbes, R. P., and Dandy, W. E.: Bilateral congenital cerebral arteriovenous communication aneurysm. Tr. Am. Neurol. Assn. 1937, p. 173.
16. Rosenberg, A. W.: A vascular malformation drained by the great vein of Galen. Bull. Los Angeles Neurol. Soc. 20:196, 1955.
17. French, L. A., and Peyton, W. T.: Vascular malformations in region of the great vein of Galen. J. Neurosurg. 11:488, 1954.
18. Logue, V., and Monckton, G.: Posterior fossa angiomas. A clinical presentation of nine cases. Brain 77: 252, 1954.
19. Clarke, E., and Walton, J. N.: Subdural hematoma complicating intracranial aneurysm and angioma. Brain 76:378, 1953.
20. Norlen, G.: Arteriovenous anomalies of the brain. Report of ten cases of total removal of the lesion. J. Neurosurg. 6:475, Nov. 1949.
21. Gillingham, J.: Arteriovenous malformations of the head. Edinburgh M. J. 60:305, 1953.
22. Foltz, E. L., and Ward, A. A.: Communicating hydrocephalus from subarachnoid bleeding. J. Neurosurg. 13:546, 1956.
23. Osler, W.: On the systolic brain murmur of children. Boston Med. & Surg. J. 103:29, 1880.
24. Dodge, H. W.: Cephalic bruits in children. J. Neurosurg. 13:527, 1956.
25. Richardson, C., and Kofman, O.: Cranial bruit with intracranial saccular aneurysms. Tr. Am. Neurol. A. 76:151, 1951.
26. Fisher, C. M.: Cranial bruit associated with occlusion of the internal carotid artery. Neurology 7:299, 1957.
27. Bassett, R. C.: Surgical experiences with arteriovenous anomalies of the brain. J. Neurosurg. 8:59, 1951.
28. Hayne, R. A., Kempe, L. G., and Coxe, W.: The surgical treatment of arteriovenous malformations of the brain. J. Neurosurg. 12:259, 1956.
29. Falconer, M. A.: Surgical pathology of intracranial hemorrhage due to aneurysms and arteriovenous malformations. Proc. Roy. Soc. Med. 47:693, 1954.
30. Javid, M., and Settlage, P.: Effect of urea on cerebrospinal fluid pressure in human subjects. J.A.M.A. 160:943, 1956.
31. Pilcher, C., Meacham, W. F., and Cobb, C. A.: The surgical treatment of intracranial angiomatous malformations. Surgery 28:342, 1950.

■ The palsy which follows apoplexy is generally a complete hemiplegia; but this is not always the case. We find in authors a very great variety of hemiplegiac anomalies, if I may so call them; and I think that I cannot better illustrate the history and the nature of this disease, than by giving an account of those cases which appear the most varied and the most extraordinary in their symptoms. Sauvages, from Conrad Fabricius, speaks of an hemiplegia which he calls *transverse*, in which one arm and the foot on the opposite side were paralytic. This species of hemiplegia, he says, frequently is the consequence of a malignant epidemic dysentery, prematurely suppressed by astringents and opiates. He adds, the rationale of this is obscure. Ramazzini speaks of a person in whom one leg had lost its feeling, but not its power of motion, and the other its motion, but not its feeling.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Prolonged Effects of Reticular Formation Stimulation on Reflex Action

Kiyomi Koizumi, M.D., Isamu Suda, M.D.* and Chandler McC. Brooks, Ph.D.

TETANIC STIMULATION of the reticular formation for only a few seconds (15 sec.) elicits inhibitory and/or facilitatory effects on spinal reflexes which persist for minutes (2 to 5 min).[1,2] Within limits, the higher the rate of stimulation the greater the effect of tetanus, but even a single rectangular stimulus pulse (3 to 8 msec.) produces changes in response which last for well over 100 msec.[3] Single pulse stimulation, which permits a more controllable study of the results of this exciting region of the brain, reveals that these effects are invariably a mixture of inhibition and facilitation. The influences on monosynaptic and polysynaptic reflexes of stimulation of a single point in the reticular formation differ. Observations such as these raise at least three questions. What is the site and nature of the inhibitory and facilitatory action exerted by the reticular formation? Why do the effects persist for so long after stimulation? What contributions do other regions of the brain make to this so-called reticular formation activity? The work herein described represents an approach to the last-mentioned problem.

METHODS

Single rectangular pulses (3 to 8 msec. in duration and 5 to 8 volts in intensity) delivered through a concentric electrode from a Grass stimulator were used to excite the suprabulbar regions of the reticular formation of cats lightly anesthetized with Nembutal (30 mg. per kg.). Glass capillary electrodes (3M KCl-filled; 20 to 35 megohms resistance when measured in 3M KCl) and larger diameter (2 to 5 microns) silver wire electrodes sealed in glass capillaries recording through the usual cathode followers and A.C. or D.C. amplifiers were used to detect unit activity within the lower bulbar regions and from descending fibers in the lateral columns of the cord. The ventral roots of seventh lumbar and first sacral segments of the cord were used to pick up the reflex action induced by stimulation of peripheral afferent fibers of muscle (gastrocnemius and biceps), skin (sural), and mixed nerves (tibialis posterior and peroneal) of the leg. After the effects obtained from stimulation of the reticular formation with the brain intact were observed, certain structures were removed and various afferent nerves were cut to determine their possible roles in the phenomena recorded.

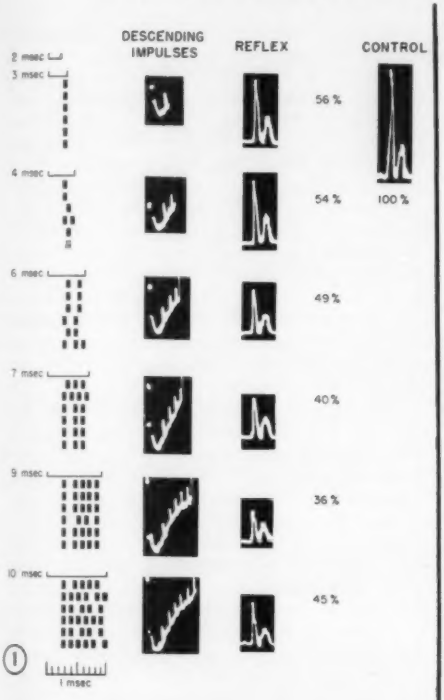
RESULTS

Single shocks of short duration did not initiate any descending impulses from the reticular formation and had no effect on the reflex. As the duration of the stimulus pulse was progressively increased from a minimum effective duration of 2 to 10 msec., the number of discharges recorded from single units in the medullary region increased. Figure 1 shows that, associated with this increase in number of descending volleys, there was an augmentation of the inhibitory or facilitatory influence on the reflex.

Stimulation of the reticular formation occasionally produced a discharge of impulses at the ventral roots of the reflex pathway under study. This, of course, affected the very early post-stimulation reflex responses, but the total effect of the reticular formation stimulation was not significantly modified. Decerebration often eliminated this early directly induced motoneuron discharge without changing the nature of the long-lasting response, thus tending to confirm this statement.

The effects of even brief single shock stimuli were a mixture of inhibition and facilitation.[4] Figure 2 shows that the duration and the time of occurrence of predominance of the two phases of the dual action varied with the reflex under study. In general these effects of a single 5 msec. stimulus on the spinal reflex persisted for more than 100 msec. When employing the monosynaptic reflex evoked by excitation of gastrocnemius muscle afferents, stimulation of a point in the reticular formation produced a 30 to 40 msec. period of inhibition, which was followed by 100 msec. of

From the department of physiology, State University of New York College of Medicine, New York City.
This work was supported by a grant from the National Institutes of Health, Public Health Service (PHS-B-847C).
*Visiting professor from the department of physiology, Kobe Medical School, Japan.
Read at the ninth annual meeting of the American Academy of Neurology, Boston, April 25, 1957.



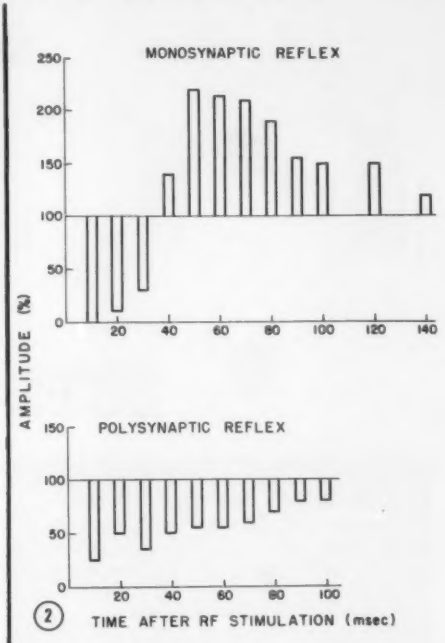


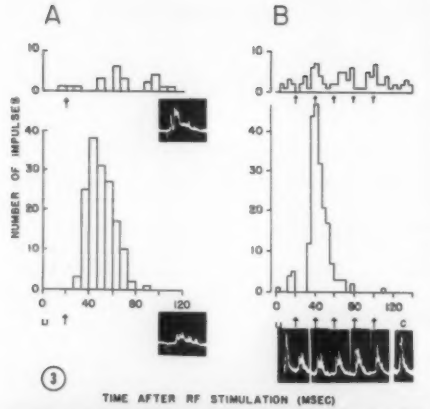
FIG. 1. Left hand column shows the latencies and the number of descending spikes in single units of the medulla after stimulation of the reticular formation with square pulses of increasing duration (six instances shown for each stimulus duration). Second column shows examples of actual records taken; third column shows inhibitory effects on the reflex simultaneously recorded. The percentages shown relate the average size of the inhibited reflex spikes to the height of the control (100 per cent).

FIG. 2. Effects of reticular formation stimulation on amplitude of spinal reflexes. Amplitude in per cent of normal (100 per cent).

facilitation. A few points were encountered from which only facilitation or inhibition were elicited, but in all cases the effects of the stimulus pulse lasted as long as 100 msec. Polysynaptic reflexes behaved somewhat differently, inhibition tending to predominate in every case even though the same stimulus evoked a late facilitatory effect on the monosynaptic reflex (figure 2).

Reticular formation control of reflex action is presumably exerted through descending reticulospinal tracts. Recordings from lateral column fibers of the lumbar spinal cord by means of microelectrodes showed two peaks of discharge following the reticular formation stimulation. The first occurred between 7 and 10 msec. and the second between 10 and 18 msec. after the stimulus.[5] The longest observed duration of the augmented descending discharge following stimulus of the reticular formation with a 5 msec. shock was 20 to 30 msec. Such recording gives no information concerning fiber function, but it is safe to assume that these descending impulses did participate in causing the observed modification of reflexes. The discharge recorded from lateral columns of the cord was not of long enough duration to participate directly in other than the early phases of stimulation after effects.

Similar recording from the medullary reticular formation showed augmented activity in units following stimulation of the suprabulbar reticular area. There was a definite latency, a time of greatest frequency, and a time limit to the evoked activity. Figures 3 and 4 show the stimulus-induced discharge recorded from two points (figure 3) following stimulation of two reticular areas and the actual records (figure 4) from which this type of time-distribu-



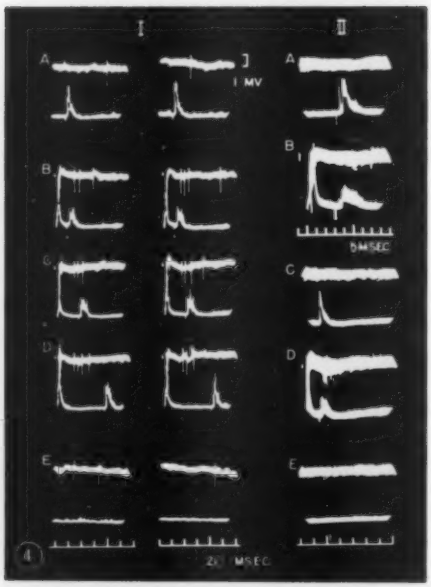
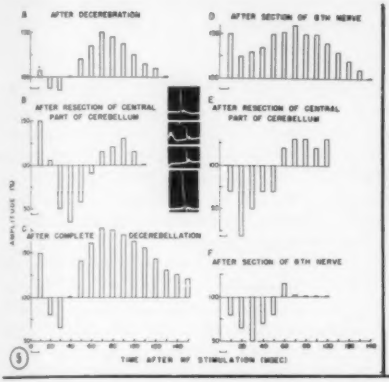
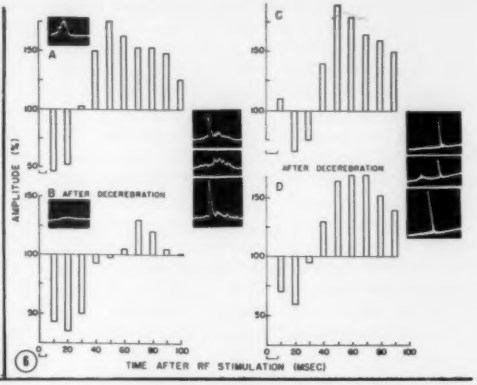


FIG. 3. Unit discharge recorded from the medullary reticular formation near obex as affected by suprabulbar reticular formation stimulation. In *A* and *B* upper graphs show background activity and lower the increase in frequency of discharge following reticular formation stimulation (⌊⌋). Inserts show reflexes as recorded from ventral roots when reflex-producing stimuli fell at the time indicated by arrow.
FIG. 4. Upper tracings are microelectrode recordings of unit activity in medullary reticular formation. Lower tracings show reflex response preceded by VR/L7 discharges due to reticular formation stimulation. *A*. Control. *B-D*. Reflex responses at various times after reticular formation stimulation. *E*. Basic state—no reflex evoked. *I*. Single sweeps. *II*. Shows responses in 50 superimposed sweeps. *A* and *C* controls.

tion curve was assembled. The augmentation of activity persisted for 80 msec., which is practically as long as the effects on the reflex. In some experiments the point stimulated and the area of recording showed an earlier medullary discharge, while in other experiments later peaks of discharge were found than those shown in figure 3. It cannot be said that the persistence of activity within the reticular formation is responsible for the long-lasting effects on the reflex, nor do we know how such activity could affect the reflex. It was found, however, that a 5 msec. stimulus pulse applied to the suprabulbar reticular formation evoked equally prolonged effects on both the spinal reflex and the activity of elements in the medullary reticular formation.

The numerous interconnections between the reticular formation and other brain structures make possible interactions which might prolong the effects of a single stimulus pulse. Consequently, the contribution of various portions of the brain were determined. After the effects of a stimulus had been observed, specific structures were removed and the same point again stimulated. It was found that no structure or nerve supply other than the reticular formation and its descending connections was essential to the effect produced. It can be seen from figure 5 D and F, however, that section of the vestibular nerve minimized both facilitation and inhibition. Ablation of the median areas of the cerebellum (vermis) reduced facilitation and prolonged inhibition (figure 5B), whereas removal of lateral components (crus I, crus II, the paraflocculus, and adjacent tissue) increased and prolonged facilitation while correspondingly reducing inhibition (figure 5C). Decortication and high decerebration likewise failed to abolish the effects of reticular formation stimulation, although in some instances the facilitatory after-effects were shorter in duration (figure 6). Finally, bilateral section of dorsal and ventral roots to prevent reverberation from muscle afferents had no effect on the inhibition or facilitation, despite the known feed-back potentialities of this system. Figure 7, which shows this absence of effect of root section, was obtained when using stimulation of the bulbar reticular formation to influence reflex action. Long-lasting effects were obtained from the bulbar reticular structures, just as in the case of suprabulbar stimulation. Decerebration and decerebellation had slight influence, but when the upper regions of the reticular formation were removed (figure 7D),


A AFTER DECEREBRATION
D AFTER SECTION OF 8TH NERVE
B AFTER RESECTION OF CENTRAL PART OF CEREBELLUM
E AFTER RESECTION OF CENTRAL PART OF CEREBELLUM
C AFTER COMPLETE DECEREBELLATION
F AFTER SECTION OF 8TH NERVE
AMPLITUDE (%)
TIME AFTER RF STIMULATION (MSEC)
9



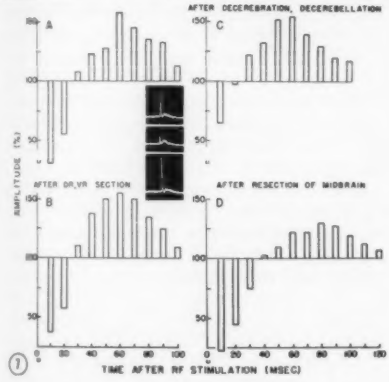


FIG. 5. Changes in effect of reticular formation stimulation on monosynaptic reflex produced by ablation of various portions of the brain or section of the vestibular nerve (*D* and *F*). *A* to *D* from one experiment and *E* and *F* from another. Insert shows normal reflex (top), reflex during inhibitions (middle two), and during phase of facilitation (lower).

FIG. 6. Two experiments showing variation in effects of decerebration. *A* and *B* from one experiment showing change; *C* and *D* from experiment in which decerebration did not significantly alter effects of reticular formation stimulation on reflex. Inserts to left show VR/L7 response to reticular formation stimulation. Other inserts show reflex response; control, inhibitory phase, facilitation after reticular formation stimulus.

FIG. 7. *A*. Effect of medullary reticular formation stimulus on monosynaptic reflex in intact animal (insert shows reflex—normal, inhibited, facilitated). *B*, *C*. and *D*. Effects of same stimulus after various ablations done in sequence shown. All roots sectioned bilaterally from L4 to S2, except DR/L7 on right side through which afferent stimuli were coming from sectioned afferent nerves.

stimulation of the medullary reticular formation produced different effects than previously. The inhibitory component of the diphasic response was increased and facilitation was diminished. Changing the sequence of these ablations and transections did not alter the conclusions drawn and here stated.

These ablation experiments indicated that subsidiary structures, acting either through reverberating pathways or by a tonic effect on the reticular formation, influence its inhibitory and facilitatory actions upon reflex responses. Stimulation of these structures has also been found to modify reticular formation effects.

A more complete analysis of the manner in which other components of the nervous system cooperate with or are involved in reticular formation functions will require extensive supplementary use of stimulation and recording technics and possibly the study of chronic preparations.

The reticular formation is an extensive, ill-defined region. It is possible that interactions within its complex structure might be responsible for the duality of action and the prolonged after-effects of stimuli. It has already been mentioned that activity can be picked up in the medullary reticular formation for many milliseconds after suprabulbar stimulation. It has also been observed that, after ablation of the reticular formation of the midbrain and areas ahead thereof, stimulation of the medullary reticular formation produces more striking and long-lasting inhibitory effects on the spinal reflexes. This is evidence of interaction within this complex as suggested.[6]

DISCUSSION

Single pulse stimulation of the reticular formation as well as tetanic excitation produces long-lasting facilitation and/or inhibition. The mixed nature of these effects and their long

duration have not easily been explained. Thus far it has not been possible to prove that the long duration of effects is due to reverberation from cerebellum, cerebral cortex, or subcortical regions nor to descending discharges from the reticular formation. Evidence was obtained of long-lasting activity within the reticular formation which might have acted caudally through fibers from which we did not record. Another possible explanation of the persistence of and the duality of influence might be as follows: Stimulation of the reticular structure does affect spinal neurons and interneurons directly.[5] The long-lasting after effects of subliminally-excited cells may contribute to the change in reflex response at the spinal level.[7]

Although facilitatory and inhibitory actions are often generalized, affecting several reflex pathways, the effects on a specific arc are very much localized. Inhibition in particular blocks the orthodromically-induced excitation of motoneurons without interfering with antidromic excitation.[3,5] This evidence of confinement of inhibition to a portion of a neuron presents difficulties to any suggestion of accumulation of a chemical mediator.[8] The reticular formation effect on the spinal reflex arc might, however, be in the nature of a physicochemical change at the synapse favorable to a greater localized output of mediator or to a more effective local action of the afferent signal at the synaptic junction.

SUMMARY

1. Single square-wave pulses applied to the suprabulbar reticular formation cause a dual effect on spinal reflexes. Following stimulation a brief (30 to 40 msec.) period of inhibition is followed by prolonged facilitation (80 to 100 msec.) of the monosynaptic reflex. Polysynaptic reflexes are affected differently, showing long-lasting inhibition.

2. Discharge of descending cord fibers of the lateral column occurs for 30 msec. following application of a 5 msec. stimulus pulse to the supramedullary reticular formation. Such a stimulus initiates detectable activity which persists for 80 msec.

3. A reduction in the facilitatory and inhibitory actions of reticular formation occurs when the vestibular nerve is cut. Decortication and decerebration reduce facilitation and increase inhibition proportionately. Removal of medial portions of the cerebellum likewise reduces facilitation and prolongs inhibition, but ablations of the remainder of the cerebellum or removal of lateral structures alone reduce inhibition and bring about greater facilitation. These structures are not essential to the prolonged action of reticular formation stimulation but modify its effects and their durations.

REFERENCES

1. Kleyntjens, F., Koizumi, K., and Brooks, C. McC.: Stimulation of suprabulbar reticular formation. Arch. Neurol. & Psychiat. 73:425, 1955.
2. Brooks, C. McC., Koizumi, K., and Siebens, A. A.: Inhibitory action of bulbar and spinal suprabulbar reticular formation on the spinal reflex pathways. Am. J. Physiol. 184:497, 1956.
3. Suda, I., Koizumi, K., and Brooks, C. McC.: Reticular formation influences on neurons of spinal reflex pathways. XXth Internat. Physiol. Congr. 1956, p. 389.
4. Brooks, C. McC., Koizumi, K., and Suda, I.: Studies of the origin and nature of reticular formation function. Acta Physiol. et Pharmacol. Neerl. 6:327, 1957.
5. Suda, I., Koizumi, K., and Brooks, C. McC.: Reticular formation influences on neurons of the spinal reflex pathway. J. Neurophysiol. In Press.
6. Dell, P., and Bonvallet, M.: Somatic functions of the nervous system. Ann. Rev. Physiol. 18:309, 1956.
7. Bernhard, C. G.: Slow cord potentials of opposite sign correlated to reciprocal functions. Acta physiol. scandinav. 14: Suppl. 47, 1947.
8. Purpura, D. P.: A neurohumoral mechanism of reticulocortical activation. Am. J. Physiol. 186:250, 1956.

Alterations in Blood Gases During Natural Sleep and Narcolepsy

A Correlation with the Electroencephalographic Stages of Sleep

Richard I. Birchfield, M.D., Herbert O. Sieker, M.D. and Albert Heyman, M.D.

ALTHOUGH the physiologic changes occurring in sleep have been the subject of much investigation, alterations in blood gases associated with sleep are still poorly understood. Mangold and his colleagues, in a recent study,[1] showed that respiratory acidosis was present in fatigued subjects who readily fell asleep, but that sleep itself was unaccompanied by changes in arterial blood gases. Endres and other workers[2,3] had previously found an increase in carbon dioxide tension during sleep. This, however, has been related to a rhythmic nocturnal elevation of alveolar carbon dioxide which occurs independently of sleep.[4] Doust and Schneider,[5] using the ear oximeter, demonstrated that moderate hypoxia appeared during sleep and they have drawn parallels between the physiologic changes seen in sleep and those noted in anoxia. These variable findings may be due to failure to correlate blood gas changes with the depth and duration of sleep or with the alterations in ventilation known to appear in the sleeping state.

All of the above observations have been made in natural sleep; it seemed likely that comparison of normal and pathologic sleep states might produce more definitive information. This study reports our observations on the alterations in arterial blood gases before, during, and on awakening from natural sleep. These findings are compared with those found in the sleep states of narcoleptic patients and are correlated with the depth of sleep as determined by the electroencephalogram. In subsequent papers the changes in ventilation during sleep and the factors influencing respiratory function in patients with narcolepsy will be considered.[6]

CASE MATERIALS AND METHODS

Observations during sleep were made on 11 male control subjects ranging in age from 21 to 26 years. Nine of the subjects were healthy medical students; the remaining two were ambulatory hospital patients with no evidence of sleep abnormalities or brain damage. No special measures were used to produce fatigue and no medications were given to induce sleep. The studies were begun between 9:30 and 10:30 p.m., the subjects usually falling asleep between 11:00 p.m. and midnight. In a few instances the studies were carried out in the forenoon.

Similar studies were made during sleep in eight male patients with idiopathic narcolepsy. Each of these patients gave a history of having had episodes of irresistible sleep for the previous three to 25 years. The number of attacks of sleep varied from two or three times a day to as many as 20 or 30 times a day. They were generally light in nature and of short duration and were usually associated with meals or monotonous activities, such as sitting in church, driving, or reading. The diagnosis of narcolepsy was supported by the presence of concomitant cataplexy in seven of these subjects, hypnagogic hallucinations in five, and sleep paralysis in four. Physical and neurologic examinations were normal, except for pulmonary emphysema in one patient and obesity (weight greater than 200 pounds) in four others. The routine laboratory studies, skull films, and electroencephalograms were normal. Pulmonary function tests were done on six of the patients and revealed no definite evidence of impaired function, except for one patient with emphysema (*J.E.*) and another with marked obesity (*M.A.*). Because of the ease with which these patients fell asleep, their studies were carried out during the daytime, usually in the forenoon.

Arterial blood samples were taken in oiled heparinized syringes from an indwelling Cournand needle inserted into the brachial artery and connected to a manifold by polyethylene tubing. Electroencephalographic electrodes

From the department of medicine (neurology and pulmonary divisions), Duke University Medical Center, and the Veterans Administration Hospital, Durham, North Carolina.

Read at the ninth annual meeting of the American Academy of Neurology, Boston, Massachusetts, April 27, 1957.

Supported by research grant B669, National Institutes of Health, Public Health Service.

TABLE 1
CHANGES IN ARTERIAL BLOOD GASES AND pH DURING SLEEP

			Awake A Stage—EEG			Drowsy or Light Sleep B and C Stage—EEG			Deep Sleep D Stage—EEG			Aroused A Stage—EEG		
Pt.	Age	Wt.	Art. pH	pCO_2 mm. Hg	O_2 % Sat.	Art. pH	pCO_2 mm. Hg	O_2 % Sat.	Art. pH	pCO_2 mm. Hg	O_2 % Sat.	Art. pH	pCO_2 mm. Hg	O_2 % Sat.
CONTROL SUBJECTS														
G.G.	23	158	7.380	45.6	95.5	7.358	48.3	94.2	7.330	51.9	93.9	7.380	43.6	96.7
J.G.	22	186	7.410	40.9	97.1	7.347	48.6	96.4	–	–	–	7.394	42.6	97.7
P.H.	23	–	7.378	43.3	95.9	7.343	46.6	96.9	7.340	47.5	96.7	7.381	42.8	97.5
J.L.	24	152	7.374	46.4	97.6	–	–	–	7.347	48.5	95.4	7.354	47.5	95.7
B.N.	25	170	7.358	47.2	98.8	7.296	55.9	93.8	7.310	53.3	99.0	7.372	43.8	100.0
J.S.	21	160	7.380	42.6	97.2	7.350	47.5	95.7	–	–	–	7.370	44.9	95.3
E.D.	23	168	7.388	43.7	96.4	7.331	51.6	93.3	–	–	–	7.364	46.2	97.1
W.R.	26	156	7.386	43.6	94.8	7.353	47.0	–	7.320	50.9	95.7	–	–	–
J.M.	21	187	7.365	46.6	96.0	7.330	52.5	95.1	–	–	–	–	–	–
A.C.	23	183	7.374	42.6	96.6	7.344	45.7	96.9	–	–	–	7.374	42.6	97.2
J.C.	24	172	7.374	40.6	95.5	7.332	46.6	95.0	–	–	–	–	–	–
Mean	23	169	7.379	43.9	96.5	7.338	49.0	95.3	7.329	50.4	96.1	7.374	44.3	97.1
p*						<.001	<.001		<.01	<.01				
NARCOLEPTIC PATIENTS														
J.C.	34	168	7.392	40.3	94.3	7.354	46.9	94.6	7.355	48.7	95.1	7.377	44.9	95.6
D.G.	34	216	7.307	54.2	91.4	7.294	55.5	92.1	–	–	–	7.310	53.1	93.9
W.E.	52	147	7.377	46.0	94.1	7.364	47.3	–	7.366	48.4	93.5	7.398	42.7	96.5
A.R	38	210	7.430	37.9	94.5	7.423	38.4	94.0	–	–	–	7.390	41.6	95.9
J.E.	60	175	7.371	48.4	90.0	7.337	52.3	88.9	7.310	56.5	88.9	7.319	53.6	92.8
H.M.	27	185	7.372	47.0	94.3	7.354	48.8	95.3	–	–	–	7.360	–	94.6
M.A.	24	290	7.330	50.0	90.1	7.315	50.6	92.1	–	–	–	7.358	48.5	91.8
H.J.	30	202	7.333	52.8	95.8	7.333	52.6	96.2	–	–	–	7.328	52.2	97.3
Mean	37	199	7.364	47.1	93.1	7.347	49.1	93.3	7.344	51.2	92.5	7.355	48.1	94.8
p*						<.01	<.05							

*Statistically significant difference from mean values of same subjects while awake.

were attached to the scalp with colloidion in standard positions. The subjects were made comfortable in bed and the initial arterial blood sample was taken after each subject had been supine for at least 20 minutes to avoid the changes in carbon dioxide tension known to appear with change in position.[7] Following this, the room was darkened and quieted and the subject was allowed to fall asleep. Repeat arterial blood samples were drawn during various stages of sleep, monitored by continuous electroencephalographic recordings. To avoid the blood gas changes which occur with periodic respirations, the respiratory pattern was monitored by means of a conventional pneumograph synchronously recorded with the electroencephalogram. Samples were taken over 30 to 60 second periods during regular breathing. An awakening sample of arterial blood was drawn immediately after the subject aroused but before any change in position occurred.

The depth of sleep was classified by the Simon and Emmons modification of the electroencephalographic stages of sleep, originally described by Loomis and co-workers.[8,9] The relaxed awake, or *A* stage, is characterized by more or less continuous alpha rhythm; the drowsy state, or *B* stage, by low amplitude activity and the absence of alpha rhythm; light sleep, or *C* stage, by 14 to 16 per second sleep spindles and/or random theta or delta waves; in deep sleep, the *D* stage, there are chains of synchronous delta activity. None of our subjects showed evidence of very deep sleep, or the *E* stage, in which there is increased voltage and continuous delta activity. The periods of sleep in narcoleptic patients lasted approximately 10 to 20 minutes, whereas those in the control subjects were usually deeper and more prolonged (45 minutes to one hour).

Blood oxygen content and saturation were determined by the photometric method of Hickam and Frayser.[10] Blood carbon dioxide was determined by the method of Van Slyke and Neill.[11] The pH of whole blood was measured with a Cambridge model R pH meter with enclosed glass electrode; measurements were corrected to 37° C., using Rosenthal's factor.[12] Plasma carbon dioxide content was calculated from the blood carbon dioxide

content, pH, and hemoglobin, using the line chart of Van Slyke and Sendroy.[13] Carbon dioxide tension was calculated from this value using the Henderson-Hasselbach equation. All determinations were done in duplicate.

RESULTS

The determinations of arterial carbon dioxide tension, oxygen saturation, and pH during wakefulness and sleep in the control and narcoleptic subjects are shown in table 1. *B* and *C* stages of sleep are considered together, since the values for blood gases were essentially the same. In the awake state, the arterial carbon dioxide tension in patients with narcolepsy tended to be higher than in the control subjects, the mean values being 47.1 and 43.9 mm. of Hg, respectively ($0.1 > p > 0.05$). Three patients with narcolepsy had values of arterial carbon dioxide tension of 50 mm. Hg or more. Only one (*M.A.*) had evidence of impaired pulmonary function, but all three weighed more than 200 pounds.

During sleep the control subjects showed a significant increase in carbon dioxide tension, with a mean change from 43.9 to 49.2 mm. Hg for all stages of sleep (figure 1 ($p < 0.001$). The narcoleptic patients, however, showed less change during sleep, with a mean rise of 47.1 to 50.1 mm. Hg ($0.05 > p > 0.02$).

In the individual control subjects the changes in arterial carbon dioxide tension occurred very

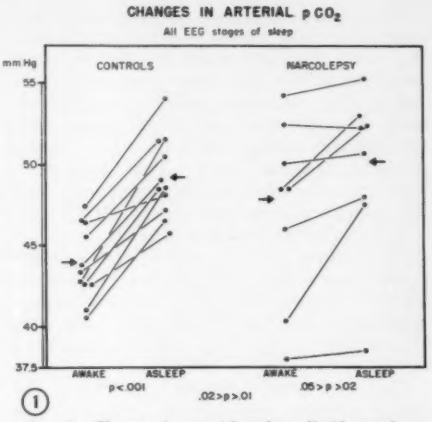
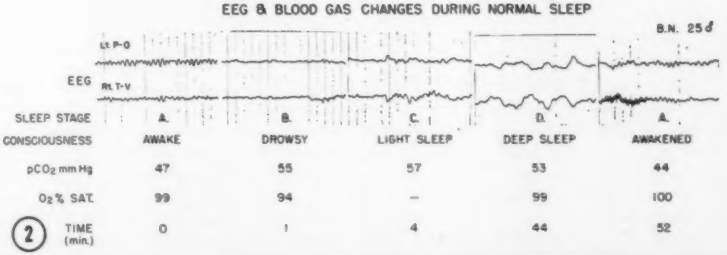


FIG. 1. Changes in arterial carbon dioxide tension observed during sleep (all electroencephalographic stages) in control subjects and narcoleptic patients. Arrows indicate the mean values for each group.


EEG & BLOOD GAS CHANGES DURING NORMAL SLEEP
B.N. 25 ♂
Lt P-O
EEG
Rt T-V
SLEEP STAGE A. B. C. D. A.
CONSCIOUSNESS AWAKE DROWSY LIGHT SLEEP DEEP SLEEP AWAKENED
pCO_2 mm Hg 47 55 57 53 44
O_2 % SAT. 99 94 – 99 100
2 TIME (min.) 0 1 4 44 52

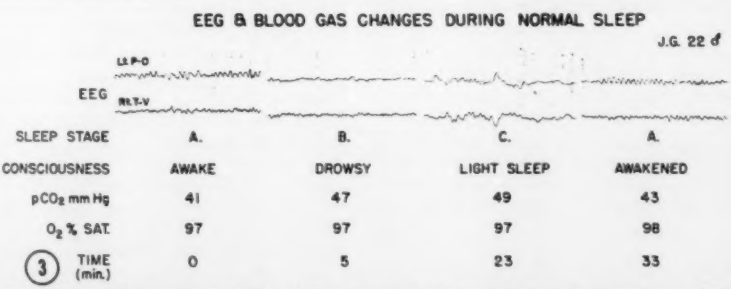

EEG & BLOOD GAS CHANGES DURING NORMAL SLEEP
J.G. 22 ♂
Lt P-O
EEG
Rt T-V
SLEEP STAGE A. B. C. A.
CONSCIOUSNESS AWAKE DROWSY LIGHT SLEEP AWAKENED
pCO_2 mm Hg 41 47 49 43
O_2 % SAT. 97 97 97 98
3 TIME (min.) 0 5 23 33

FIG. 2. Changes in blood gases during the various electroencephalographic stages of normal sleep. Time is measured from the onset of sustained drowsiness.

FIG. 3. Changes in blood gases during the various electroencephalographic stages of normal sleep. Time is measured from the onset of sustained drowsiness.

early during sleep, usually in the drowsy or *B* stage, sometimes appearing within a few minutes after the electroencephalographic manifestations of this transitional state (figures 2 and 3). The narcoleptic patients, on the other hand, showed only a very slight carbon dioxide retention during either the *B* or *C* stages of sleep (figures 4 and 5). With deep sleep, however, both the narcoleptic patients and the control subjects showed a slight increase in carbon dioxide tension (table 1).

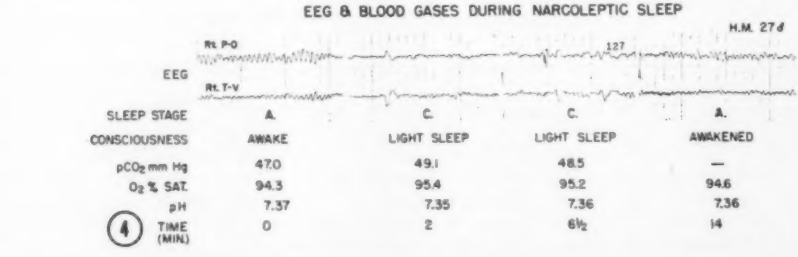
The arterial pH was slightly lower in the awake narcoleptic patients than in control subjects. During sleep, however, there was a significant fall in arterial pH in both the control subjects ($p < 0.001$) and in the narcoleptics ($0.01 > p > 0.001$).

The mean arterial oxygen saturation in the control subjects, while awake, was 96.5 per cent, as compared to 93.1 per cent in the narcoleptic patients ($0.01 > p > 0.001$). During all stages of sleep, the mean value for oxygen saturation showed a slight but significant fall in the control subjects ($0.05 > p > 0.02$) and no change was noted in the narcoleptic patients (figure 6).

On arousal, both the control subjects and the narcoleptic patients showed a prompt return of blood gas determinations to values similar to those noted prior to sleep. A few of the control subjects showed a further decrease in carbon dioxide tension, with an elevation of oxygen saturation indicating that they hyperventilated at the time of arousal.

DISCUSSION

The retention of carbon dioxide and the slight decrease in arterial oxygen saturation, which occur with drowsiness prior to natural sleep and persist throughout deep sleep, are probably due to hypoventilation which occurs during these states of consciousness. The rapid return of blood gases to normal with arousal suggests that respiratory function is directly related to the state of awareness and that the respiratory center is dependent upon the afferent stimuli in wakefulness to maintain an optimal level of blood gases. Studies in our laboratory and those of Robin and his coworkers,[6,14] however, have shown that the inhalation of carbon dioxide during sleep produces less ventilatory stimulus than in the awake state, indicating that the hypercapnia in sleep is related to a decrease in respiratory center sensitivity. There is also evidence that, during sleep, there is a decrease in tidal vol-



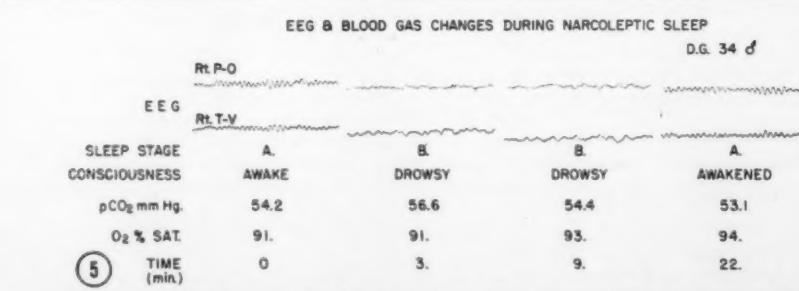


FIG. 4. Changes in blood gases during sleep in narcolepsy. Time is measured from the onset of sustained drowsiness.

FIG. 5. Changes in blood gases during sleep in narcolepsy. Time is measured from the onset of sustained drowsiness.

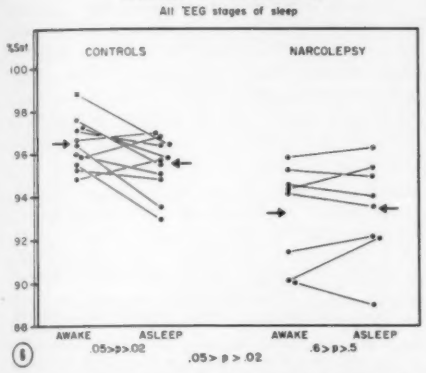


FIG. 6. Changes in arterial oxygen content observed during sleep (all electroencephalographic stages) in control subjects and narcoleptic patients. Arrows indicate the mean values for each group.

ume and alveolar ventilation.[6] The relative importance of these factors in producing the observed changes of blood gases in sleep is now being studied.

The hypercapnia and the mild hypoxia observed in our narcoleptic patients while awake is worthy of note, since the findings of Mangold and his colleagues[1] suggested some relationship between respiratory acidosis and the process of falling asleep. On the other hand, the level of carbon dioxide tension in our patients did not exceed 60 mm. Hg, and considerably higher levels are frequently seen without somnolence in patients with pulmonary insufficiency due to emphysema.[15] In all probability, mild hypercapnia and hypoxia in the awake narcoleptic are the result of a moderate degree of hypoventilation caused by disordered function in the central nervous system, that is, either decreased awareness with fewer afferent stimuli or a diminished respiratory center sensitivity. We have observed evidence of decreased response to sensory stimuli in narcolepsy. This consisted of failure of painful cutaneous stimuli to obliterate the alpha rhythm of the electroencephalogram during cataplectic episodes. It appears, therefore, that the narcoleptic patient, while awake, has functional disturbances in the central nervous system which may be similar to those in normal subjects while asleep (that is, he may be as if on the verge of sleep).

An understanding of the relationship of hypersomnolence to the changes in ventilation must take into consideration the factor of varying degrees of obesity which were present in four of our eight patients with narcolepsy. The association of abnormal sleep states with obesity has been commented upon recently in several reports of an obesity cardiopulmonary syndrome, or the so-called Pickwickian syndrome.[16,17] The mechanism for somnolence in the cardiopulmonary syndrome is poorly understood, but it seems not unlikely that our group of narcoleptic patients, at least those who were overweight, may represent "formes fruste" of the extreme examples of obesity and somnolence now being reported. The abnormalities of blood gases and pulmonary function in our patients with narcolepsy were found to be considerably less severe than those present in the patients with the Pickwickian syndrome.[6,16] Although congestive heart failure, pulmonary insufficiency, Cheyne-Stokes respiration, and right axis deviation of the electrocardiogram are not usually observed in narcolepsy, polycythemia is occasionally observed in both narcoleptic and Pickwickian patients. Considerable attention has been given to somnolence in the Pickwickian syndrome, but there is no mention in the case reports of such narcoleptic manifestations as cataplexy, sleep paralysis, and hypnagogic hallucinations. Nevertheless, there seem to be sufficient clinical and physiologic similarities between certain patients with narcolepsy and those with cardiopulmonary syndrome to suggest common pathogenetic mechanisms.

Whether the retention of carbon dioxide or the decrease in arterial oxygen content observed during sleep plays any role in the production of certain nocturnal symptoms, such as nocturnal epilepsy, night cramps, paroxysmal hemoglobinuria, nocturnal angina, and the like, remains speculative. The degree of elevation of carbon dioxide tension observed during sleep, although small, has been found sufficient to produce changes in cerebral circulation and possibly in other physiologic functions.[18] More severe degrees of hypoxia may appear during sleep in the aged, in patients with organic diseases of the nervous system, and in drug intoxications, and may account for the occurrence of nocturnal confusion frequently seen in these individuals. Studies are now being carried out to explore these possibilities.

CONCLUSIONS

1. Changes in arterial oxygen saturation, carbon dioxide tension, and pH occurring before, during, and on awakening from sleep

were studied in 11 normal subjects and eight patients with narcolepsy. These changes were correlated with the electroencephalographic stages of sleep.

2. In normal subjects, retention of arterial carbon dioxide and a decrease in arterial oxygen content appeared with the earliest electroencephalographic changes of drowsiness and persisted throughout deep sleep. The narcoleptic patients, while awake, tended to show values for blood gases similar to those seen in normal subjects while asleep.

3. It is suggested that respiratory function in man is directly dependent upon the state of awareness. The mild hypercapnia and hypoxia observed in normal subjects while asleep and in narcoleptic patients while awake may be due to a decrease in afferent stimuli or a diminished sensitivity of the respiratory center during these states of consciousness.

We are indebted to Mrs. Mary Ruth Greenfield and Miss Corinna Thomas for their valuable technical assistance.

REFERENCES

1. Mangold, R., Sokoloff, L., Conner, E., Kleinerman, J., Therman, P. G., and Kety, S.: The effects of sleep and lack of sleep on the cerebral circulation and the metabolism of normal young men. J. Clin. Investigation 34:1092, 1955.
2. Endres, G.: Atmungsregulation und Blutreaktion im Schlaf. Biochem. Ztschr. 142:53, 1923.
3. Kleitman, N.: Sleep and Wakefulness As Alternating Phases in the Cycle of Existence. University of Chicago Press, Chicago, Ill., 1939.
4. Mills, J. N.: Changes in alveolar carbon dioxide tension by night and during sleep. J. Physiol. 122:66, 1953.
5. Doust, J. W. L., and Schneider, R. A.: Studies in the physiology of awareness: Anoxia and the levels of sleep. Brit. M. J. 1:449, 1952.
6. Heyman, A., Sieker, H. O., and Birchfield, R. I.: Unpublished data.
7. Mackay, I. F. S.: Influences of posture on pulmonary blood volume and alveolar gas tensions. J. Physiol. 102:228, 1943.
8. Simon, C. W., and Emmons, W. H.: EEG, consciousness and sleep. Science 124:1066, 1956.
9. Loomis, A. L., Harvey, E. N., and Hobart, G.: Cerebral states during sleep as studied by human brain potentials. J. Exper. Psychol. 21:127, 1937.
10. Hickam, J. B., and Frayser, R.: Spectrophotometric determination of blood oxygen. J. Biol. Chem. 180: 457, 1949.
11. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry. Vol. II. Methods. Williams & Wilkins, Baltimore, Md., 1932.
12. Rosenthal, T. B.: Effect of temperature on pH of blood and plasma in vitro. J. Biol. Chem. 173:25, 1948.
13. Van Slyke, D. D., and Sendroy, J., Jr.: Studies of gas and electrolyte equilibria in blood; line charts for graphic calculations by Henderson-Hasselbach equation, and for calculating plasma carbon dioxide content from whole blood content. J. Biol. Chem. 79: 781, 1928.
14. Robin, E. D., Whaley, R. D., Crump, C. H., and Travis, D. M.: Alveolar gas concentrations and respiratory center sensitivity to CO_2 during natural sleep. Federation Proc. 16:107, 1957.
15. Sieker, H. O., and Hickam, J. B.: Carbon dioxide intoxication: The clinical syndrome, its etiology and management with particular reference to the use of mechanical respirators. Medicine 35:389, 1956.
16. Estes, E. H., Sieker, H. O., McIntosh, H. D., and Kelser, G. A.: Reversible cardiopulmonary syndrome with extreme obesity. Circulation 16:179, 1957.
17. Burwell, C. S., Robin, E. D., Whaley, R. D., and Bickelmann, A. G.: Extreme obesity associated with alveolar hypoventilation—A Pickwickian syndrome. Am. J. Med. 21:811, 1956.
18. Patterson, J. L., Heyman, A., Battey, L. L., and Ferguson, R. W.: Threshold of response of the cerebral vessels of man to increase in blood carbon dioxide. J. Clin. Investigation 34:1837, 1955.

■ The violent and general epileptic form of convulsion which attends upon death by hemorrhage or suffocation is associated with a defective and not with an excessive supply of arterial blood to one or other of the great nerve-centres. Nor is it otherwise with ordinary epileptic or epileptiform convulsion. The deathly paleness of the countenance which precedes the convulsion is, indeed, a plain proof that the fit commences in a state of circulation which is the very opposite to that of active determination of blood to the head, and the strong pulse which is usually perceptible in the arteries as the fit progresses is no contradiction to this conclusion. This strong pulse is usually regarded as a sign of arterial excitement – as a proof that more arterial blood is being injected into the arteries at this time, and that, on this account, certain nervous centres are excited to an unwonted degree of activity; but the simple fact is, that the strong pulse which is present under these circumstances derives its strength, not from arterial blood, but from venous.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

Experimental In Vitro Demyelination

Albert Schatz, Ph.D. and Lionel M. Adelson, M.S.

"In considering the pathology of multiple sclerosis, or indeed of any of the degenerative diseases of the nervous system, the mechanism of demyelination is one of the outstanding problems with which we are faced."[1] "For obvious reasons, the chemistry of the myelin destruction that accompanies Wallerian degeneration has been studied more intensively than that of other types of demyelination."[2] In this process, physical destruction of myelin sheaths is the predominant feature during the first eight days following sectioning, whereas chemical degradation occurs from the eighth to the thirty-second day.[2] Wallerian degeneration is, therefore, relatively slow compared to the demyelination accomplished overnight by certain soil microflora.[3] Such organisms would appear to be useful biologic reagents with which to investigate the chemistry of myelin degradation. This paper is concerned with applications of microbiology to the study of demyelinative phenomena.

Previous investigations revealed that 132 soil microflora catabolized various lipids and lipid derivatives.[4] However, only six actinomycetes, out of the total 132 organisms surveyed, were found to markedly demyelinate blocks of bovine spinal cord in vitro.[3] Because of this ability, these active cultures are now being exploited to develop in vitro demyelinating tests for screening chemical compounds to select agents with antidemyelinating properties. Substances effective in vitro may justify clinical trials to determine whether they interfere with demyelination in vivo. Such blocking agents may, in addition, help elucidate biochemical pathways whereby myelin is degraded. Finally, the active actinomycetes may provide enzymes and other myelinolytic substances that can be used to take myelin apart in a piecemeal manner, and thus contribute information concerning the physicochemical structure of this complex material. The present work was undertaken to study strain variation and conditions for maximal production of myelinolytic agent(s) by *Streptomyces griseus*, the most active species so far obtained.

MATERIALS AND METHODS

Cultures were grown in a modified Krebs-Ringer-phosphate basal solution[5] supplemented with 0.05 per cent $(NH_4)_2SO_4$ and 0.2 per cent of each substrate, except for the bovine spinal cord homogenate[4] which was supplied at 1.2 per cent wet weight. Static and agitated media containing 45.0 ml. and 100.0 ml. portions per 125 and 250 ml. Erlenmeyer flasks, respectively, were brought to pH 7.0 to 7.2 before sterilization.

The substrates included "pure ex ovo" lecithin (Pfanstiehl Chemical Co.) and animal cephalin (Nutritional Biochemicals Corp.), the latter being a mixture of phosphatidyl serine, phosphatidyl ethanolamine, and diphosphoinositide.[6] Crude brain sphingolipid[7] and the inositol lipid fraction from corn phosphatide[8] were kindly supplied by Dr. H. E. Carter at the University of Illinois. Proteolipid was prepared from bovine spinal cord by the procedure of Folch and co-workers.[9] B.S.C. (bovine spinal cord) lipids, supplied by Armour & Company, contained sphingomyelin, cerebrosides, and animal lecithin, but no cholesterol. Substrates were autoclaved in with the medium, except for ethanolamine; this was adjusted to pH 7.0 by H_2SO_4 and then sterilized via filtration through sintered glass.

Following incubation at 28 to 30° C., the cultures were adjusted to pH 7.1 to 7.4 by adding 0.1N NaOH, with brom thymol blue as indicator. Two blocks of fresh bovine spinal cord, approximately 1.0 cm. in length, were then immersed in each flask for 24 hours at room temperature. Controls consisted of blocks submerged in uninoculated media. The cord, obtained from the lumbar and sacral regions of cattle within an hour after slaughter, was separated from its enveloping membranes before being cut into blocks and exposed to the cultures. During the first four hours, some flasks required additional NaOH to keep the reaction within the physiologic range. After 24 hours the culture broths were carefully decanted and replaced by a 10 per cent neutral formol saline fixative. This removal and addition of fluid were carried out carefully to avoid sloughing off peripheral cord tissue that was particularly fragile due to partial degradation or loss of its myelin.

From the research laboratory, National Agricultural College, Doylestown, Bucks County, Pennsylvania.
This investigation was supported in part by Grant No. 65-2 from the National Multiple Sclerosis Society.
Read by title at the ninth annual meeting of the American Academy of Neurology, Boston, April 22-27, 1957.

The blocks were then washed, dehydrated, infiltrated, and embedded in paraffin (m.p. 56 to 58° C.) in the usual way. After this, one block from each flask was sectioned transversely and the other longitudinally. The 8 to 10 microns thick sections were stained by a modification of the Smith-Quigley technic, employing an iron alum mordant followed by freshly prepared 1.0 per cent aqueous hematoxylin. For the bovine tissue employed in these investigations, it was found advantageous to modify the conventional procedure by mordanting for only 15 minutes followed by immersion in the stain for half an hour.

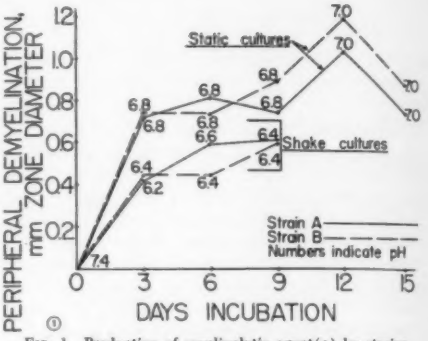


FIG. 1. Production of myelinolytic agent(s) by strains A and B of *S. griseus* No. 58 grown in a cord homogenate medium under aerated and stationary conditions. Numbers at three-day intervals on each curve are pH values of the cultures.

RESULTS

The experiments reported in figure 1 were carried out with two strains of *S. griseus* designated 58-A and 58-B. These isolates, originally picked from glycerophosphate agar plates streaked with sheep manure,[4] degraded myelin more extensively than other organisms did. Shortly after these cultures were isolated, cross-utilization tests, reported elsewhere,[4] showed that *S. griseus* 58-A and 58-B both grew on spinal cord homogenate, lecithin, cephalin, the inositol lipid, sphingomyelin, sphingolipid, proteolipid, B.S.C. lipids, a purified cerebroside, paraffin, stearate, palmitate, olive oil, bayberry wax, glycerophosphate, acetylcholine, and ethanolamine. Neither strain developed on phrenosin, cholesterol, or ethylamine. The only difference in substrate utilization was that 58-A grew on choline, whereas 58-B did not. The two cultures hemolyzed bovine erythrocytes, a reaction believed to involve breakdown of cell surface phosphatides,[10] but did not liquefy gelatin. *S. griseus* 58-A, as well as another myelin-degrading *Streptomyces*, No. 178, produced lipoproteinase(s) which caused increased turbidity in lipemic canine serum.[11]

According to results presented in figure 1, strains 58-A and 58-B exhibited essentially similar pH patterns measured at three-day intervals. In general, agitated cultures were somewhat more acid than flasks incubated statically. Demyelinating activities produced under aerated and stationary conditions were more or less parallel for the two organisms. The ability to degrade myelin was greater in static cultures where maximal potency was attained on the twelfth day of incubation. Although *S. griseus* 58-B was selected for subsequent studies, differences in the demyelinating properties exhibited by the two strains (figure 1) were not considered significant.

Table 1 shows the influence of composition of the growth medium on demyelinating ac-

TABLE 1

INFLUENCE OF COMPOSITION OF GROWTH MEDIUM ON MYELINOLYTIC ACTIVITY OF *STREPTOMYCES GRISEUS* 58-B[1]

Basal Solution Supplemented with Substrate[2]	*Observations after 12 Days Incubation*				*mm. Average Depth of Demyelinated Periphery*[3]		
	Relative Growth		*pH*		*Transverse Section*		*Longitudinal Section*
	A	*B*	*A*	*B*	*A*	*B*	*A*
Spinal cord homogenate	++	+++	7.0	7.0	0.82	2.0	1.3
Proteolipid	++		6.8		0.44		0.44
B.S.C. lipids	+++		6.8		0.44		0.44
Sphingolipid	++		6.8		<0.20		0.30
Inositol lipid	+++		6.8		0.22		<0.20
Lecithin	++++		6.6		0.37		<0.20
Cephalin	++++	++++	6.6	7.0	0.59	0.60	0.40
Glycerol	++++		<6.0		<0.20		<0.20
Ethanolamine	++	++++	6.6	7.0	0.74	1.8	0.74
Glycerol plus DL-Serine		++++		6.0		0.30	

[1]A and B represent two separate experiments.
[2]No significant growth or demyelination occurred in media containing DL-serine or choline as sole substrates.
[3]Sections from control blocks of cord immersed in uninoculated media showed no demyelination or isolated small peripheral patches of myelin degradation no more than 0.20 mm. deep. Maximum diameter of the cord sections employed ranged from 10.0 to 12.0 mm.

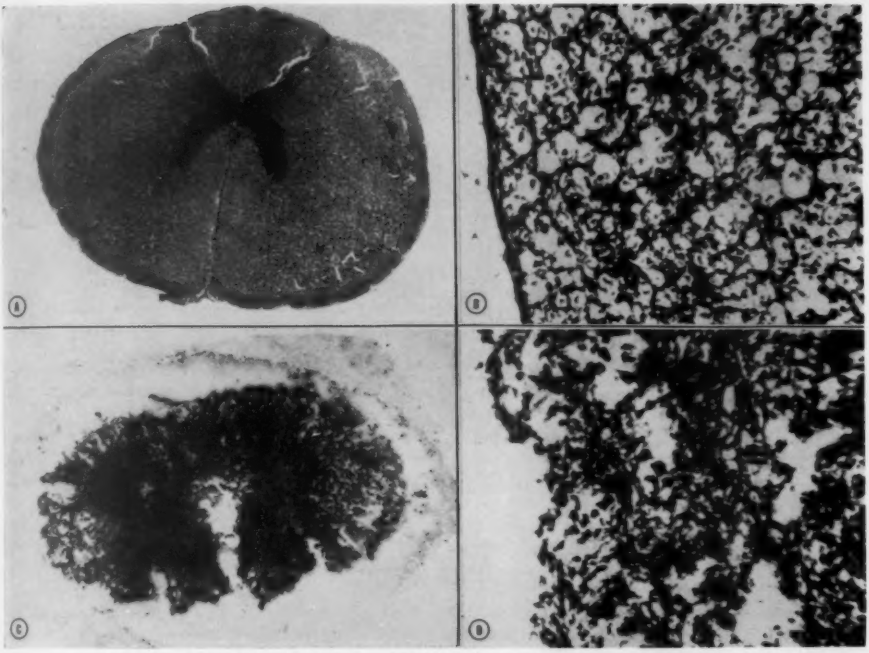


FIG. 2. Transverse sections of bovine spinal cord showing effect of exposure to *S. griseus* 58-B culture. *A* and *B* represent controls from uninoculated medium. *C* and *D* are from a block submerged in a cord homogenate culture.

tivity exhibited by whole cultures of *S. griseus* 58-B. In general, there was no correlation between myelinolytic activity and the amount of growth, which varied greatly with different substrates.

According to the results of experiment A (table 1), the glycerol culture allowed good development of the organism, but did not demyelinate to an appreciable extent. Ethanolamine, on the other hand, sustained significantly less growth than glycerol did, but gave considerably more demyelinating activity. Lecithin and cephalin, as well as sphingolipid, proteolipid, and the B.S.C. lipids, were as good or better growth substrates than ethanolamine but were less effective for production of myelinolytic agent(s). The fact that the inositol lipid was a corn phosphatide; that is, of plant origin, may explain why this substance was associated with little myelin-degrading activity. The cord homogenate culture was most myelinolytic, although proliferation of the actinomycete was less than on lecithin, cephalin, the inositol lipid, B.S.C. lipids, and glycerol.

The extent of variability in results from one experiment to another is shown in table 1. Here, cultures on cord homogenate, cephalin, and ethanolamine exhibited the same relative order of demyelinating activity for experiments A and B, even though all corresponding data were not identical.

It is apparent from experiment A (table 1) that both transverse and longitudinal sections revealed essentially the same general pattern of demyelinating activity for the different culture media. Although only one block of spinal cord was cut each way, two blocks were examined from every culture and at least two sections were prepared per block. In these studies, as in similar investigations reported by other workers,[12] there is some variation in the effects exerted by the same culture on several identically treated blocks from a single cord. But such differences are not as great as those associated with the different substrates shown in table 1.

The kinds of histologic changes observed are shown in figures 2, 3, and 4. Control cord which had been immersed overnight in un-

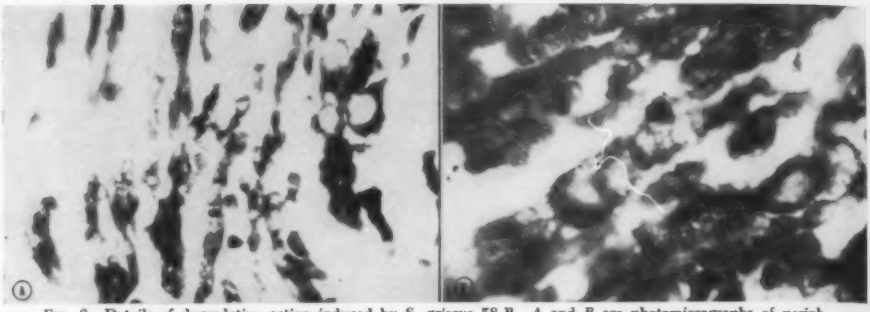


FIG. 3. Details of degradative action induced by *S. griseus* 58-B. *A* and *B* are photomicrographs of peripheral sections from figure 2 *D* taken at two higher magnifications.

inoculated media and blocks exposed to inactive cultures showed no demyelination or only small, shallow, isolated, and irregular peripheral patches. Microbial contamination from handling the cord was of little or no consequence. These observations are in accord with the chemical stability of nerve tissue over a 24-hour incubation period in vitro,[2,13] and its resistance to contaminating organisms, with the exception of *Clostridium welchii*.[13] Active cultures, on the other hand, produced deeper zones of myelin degradation which usually extended entirely around the sections and seemed to penetrate most deeply in the vicinity of the afferent pathways. These observations, however, are based on histologically observable changes. It is entirely possible, of course, that some cultures which were considered inactive may nevertheless have produced chemical changes not discernible with the staining technic employed. In other words, myelin need not necessarily be "healthy" or "normal" simply because it appears structurally intact.[14]

DISCUSSION

Although isolated constituents of myelin may be readily respired[5] and utilized as microbial growth substrates,[4,5,11] the same substances may not necessarily be susceptible to attack when they occur conjugated in intact myelin. This may partially explain why only six out of 132 cultures, which developed on phospholipids and related substances, were capable of demyelinating bovine spinal cord.[4] On the other hand, bacterial hydrolysis of phospholipid may in some cases require that the substrate be in a combined state.[15] That marked demyelination was exhibited in our studies by so relatively few organisms, all of which were actinomycetes, suggests a much greater stability of spinal cord (resistance to microfloral attack) under the experimental conditions which obtained than had been assumed *a priori*. This indicates a specific action; that is, a common mode of attack by the six actinomycetes, perhaps at one particularly vulnerable site.

If myelin were equally susceptible to degradation at several loci, one might consider demyelination as a more or less nonspecific effect. Under such circumstances, a greater percentage of cultures which grew on phospholipids and related substances[4] would probably have exhibited demyelinating properties.[3] Likewise, in the case of *S. griseus* 58-B, one might have anticipated greater myelin-degrading activity, especially by the sphingolipid and lecithin cultures (table 1). The relatively low potency of the latter indicates that lecithinase, reported by others to possess demyelinating properties,[12,16] may not be involved in the activity of *S. griseus* 58-B. Although this strain did not grow on or respire choline, which is the nitrogenous base of lecithin, it did proliferate on and oxidize lecithin itself.[5]

One is tempted to consider ethanolamine as the myelin locus vulnerable to attack by *S. griseus* 58-B. This is suggested by the highly destructive activity of the ethanolamine-grown cultures in experiments A and B (table 1). Furthermore, those media made up with cephalin and cord homogenate, both of which contain ethanolamine, were also appreciably active. Although *S. griseus* 58-B grows on cephalin and ethanolamine, it respires the former rapidly but the latter slowly.[5] However, there need be no relationship between rate of oxygen uptake in a Warburg respirometer and demyelinating activity since the latter may result from nonoxidative catabolism, or may operate under anaerobic conditions by utilizing

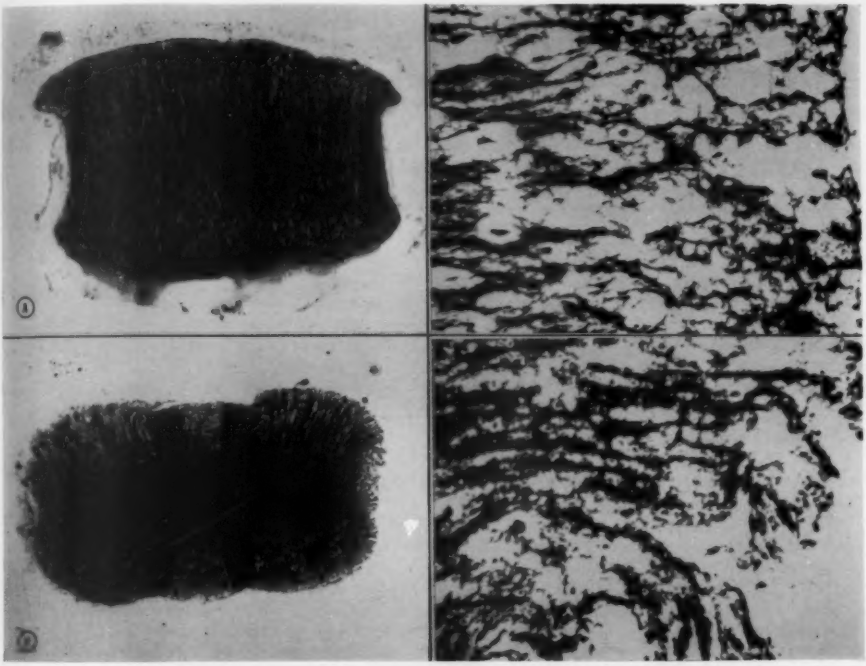


FIG. 4. Longitudinal sections of cord showing action of *S. griseus* 58-B. *A* and *B* are controls. *C* and *D* are from a block treated with a cord homogenate culture.

hydrogen acceptors other than molecular oxygen.

The inability of *S. griseus* 58-B to grow on serine alone, the low activity of the glycerol-serine culture, and the greater demyelination caused by the ethanolamine– as compared with the cephalin-grown organism tend to implicate phosphatidyl ethanolamine rather than phosphatidyl serine as the site of attack. But precise information as to agent(s) and biochemical pathway(s) involved in demyelination by *S. griseus* remains to be elucidated. Whether this breakdown is merely an accelerated Wallerian degeneration and the extent to which the lipid changes correspond to those occurring *in vivo* are not yet known.

SUMMARY AND CONCLUSIONS

Bovine spinal cord undergoes appreciable demyelination when exposed overnight to certain cultures of *Streptomyces griseus*. This soil actinomycete exhibits maximal demyelinating activity when grown for 12 days under static conditions in a modified Krebs-Ringer-phosphate liquid medium supplemented with spinal cord homogenate. The substitution of other substrates, with the exception of ethanolamine, gave appreciably less activity. The possible mechanism whereby *S. griseus* degrades myelin and the usefulness of such organisms as biologic reagents for investigating demyelinative phenomena are discussed.

REFERENCES

1. THOMPSON, R. H. S.: Esterases, lipases and phosphatases of the nervous system. Guy's Hosp. Rep. 105:93, 1956.
2. ROSSITER, R. J.: Chemical constituents of brain and nerve. Chapter 2 in Neurochemistry. Charles C Thomas. Springfield, Illinois, 1955.
3. ADELSON, L. M., SCHATZ, A., and TRELAWNY, G. S.: Demyelination of bovine spinal cord by soil actinomycetes. Bact. Proc. M67, 1956.
4. SCHATZ, A., ADELSON, L. M., and TRELAWNY, G. S.: Phospholipids and related substances as growth substrates for soil microorganisms. Appl. Microbiol. 4: 223, 1956.
5. ADELSON, L. M., SCHATZ, A., and TRELAWNY, G. S.: Metabolism of lipid and lipid derivatives by a soil actinomycete. J. Bact. 73:148, 1957.
6. FOLCH, J.: Complete fractionation of brain cephalin; isolation from it of phosphatidyl serine, phosphatidyl

ethanolamine, and diphospoinositide. J. Biol. Chem. 177:497, 1949.
7. Carter, H. E., Haines, W. J., Ledyard, W. E., and Norris, W. P.: Biochemistry of the sphingolipides. I. Preparation of sphingolipides from beef brain and spinal cord. J. Biol. Chem. 169:77, 1947.
8. Carter, H. E., Celmer, W. D., Lands, W. E. M., Mueller, K. L., and Tomizawa, H. H.: Biochemistry of sphingolipides. VIII. Occurrence of a long chain base in plant phosphatides. J. Biol. Chem. 206: 613, 1954.
9. Folch, J., Ascoli, I., Lees, M., Meath, J. A., and LeBaron, F. N.: Preparation of lipide extracts from brain tissue. J. Biol. Chem. 191:833, 1951.
10. Zamecnik, P. C., Folch, J., and Brewster, L.: Protection of animals against Clostridium welchii (Type A) toxin by injection of certain purified lipids. Proc. Soc. Exper. Biol. & Med. 60:33, 1945.
11. Schatz, A., Adelson, L. M., and Bailey, C. P.: Microbial degradation of aorta plaque lipids, lipoproteins and related substances. J. Appl. Bact. 20:30, 1957.
12. Morrison, L. R., and Zamecnik, P. C.: Experimental demyelination by means of enzymes, especially the alpha toxin of Clostridium welchii. Arch. Neurol. & Psychiat. 63:367, 1950.
13. Johnson, A. C., McNabb, A. R., and Rossiter, R. J.: Lipids of the nervous system during in vitro degeneration. Canad. J. Res. 27:63, 1949.
14. Edgar, G. W. F.: The investigation of demyelinating diseases and quantitative determination of myelin lipids. Monatsschr. Psychiat. u. Neurol. 131:274, 1956.
15. Zwartouw, H. T., and Smith, H.: Non-identity of the phospholipase of Bacillus anthracis with the anthrax toxin. J. Gen. Microbiol. 15:261, 1956.
16. Frazer, A. C., Elkes, J. J., Sammons, H. G., Govan, A. D. I., and Cooke, W. T.: Effects of Cl. welchii type A toxin on body tissues and fluids. Lancet 1:457, 1945.

■ Nowadays ataxy is not considered to be a necessary symptom of tabes; when present, it is a subordinate, although a very striking one; it is a less serious trouble than tabetic amaurosis, and is far less serious to life than the bladder disorder in this disease. Frequently cases of what are called tabes are reported as being complicated with symptoms from other types, progressive muscular atrophy, lateral sclerosis, etc. There is what Gowers well calls "ataxic paraplegia." We have under the name of Friedreich's disease a series of cases which at one extreme merges into tabes, and at the other into disseminated sclerosis. These remarks show that the set of diseases spoken of are studied by type; one hears such expressions as "a typical case of tabes," this expression implying that there are also atypical cases (subtypical and supertypical). They show, too, that the types are arbitrary. Some may say that they dislike arbitrary divisions; but when we cannot distinguish, we must, for purposes of practice, divide; even in purest science arbitrary definitions are necessary; the mathematician's line has no breadth.

J. Hughlings Jackson in *Remarks on the Diagnosis and Treatment of Diseases of the Brain*, published in 1888.

Clinical Significance of Impairment of Sound Localization

Luis P. Sanchez-Longo, M.D. and Francis M. Forster, M.D.

IN A RECENT REPORT a clinical test for sound localization was proposed.[1] The world literature concerned with the physical, psychologic, and neurophysiologic factors governing the function of sound localization was reviewed. After studying a series of normal subjects, five cases of temporal lobe lesions were reported in which there was impairment of localization of sound in the contralateral auditory field. The test was offered as a simple clinical mean to localize lesions of the temporal cortex.

This is a follow-up study, including a larger normal series and 50 cases of different etiologies and sites of involvement.

METHOD AND PROCEDURE

Using the same method and procedure as described in the earlier report,[1] the series of normal subjects was expanded to 50. Patients were examined the same way, with the difference that in hemiplegic cases the entire test was performed with the normal hand alone. It has been observed previously that normal individuals, either right- or left-handed, can perform a normal test when using either hand alone. Besides, as it will be shown in the results of the present series, hemiplegic patients without temporal lobe damage perform normally.

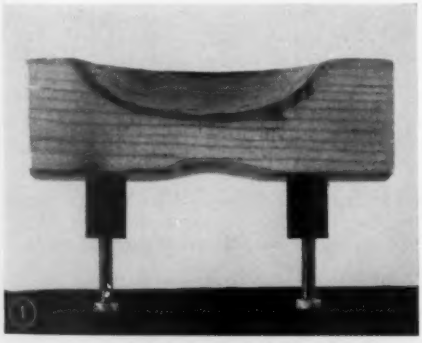


FIG. 1. The chin rest in use at the present time is made from a small block of wood, with a concavity for the chin and two adjustable screws to attach it to the perimeter chin rest. It is comfortable and helps to maintain equal distances from the ears to the edge of the perimeter.

Without repeating the entire procedure, we will mention here the most important aspects of testing. The patient should be able to understand the test to be performed. If he is greatly confused or if his I.Q. is low enough to impair his understanding, the test should not be done. The subject faces an eye perimeter, with the chin supported and with the ears at equal distances to the edge of the perimeter. For this purpose we have used a modified chin rest which the subject finds more comfortable (figure 1). The subject is blindfolded and at no time is he permitted to move his head. He should be instructed to point exactly at the spot where he thinks the sound is coming from. The sound is the low frequency masking sound of an audiometer, coming from a receiver (earphone) which is placed at 13 different standard positions at the edge of the perimeter. The patient should be able to hear the sound with both ears. Subjects having a

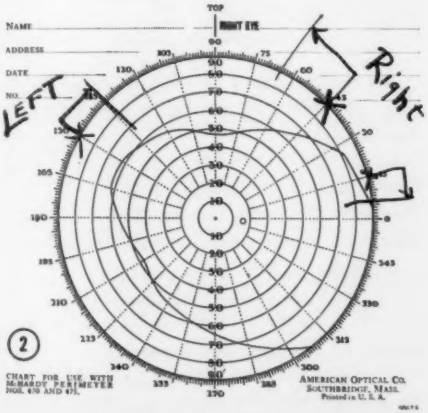


FIG. 2. The peripheral visual field chart used to record performance in this test. It is labeled left and right for the corresponding fields. The record above indicates that the subject pointed to the angle labeled 135 for a sound coming from the angle 150 on the left. The angular deflection for this particular position is 15 degrees. Two positions in the right were tested with angles of deflection of 20 and 9 degrees.

From the department of neurology, Georgetown Medical Center, Washington, D.C.

Read at the ninth annual meeting of the Academy of Neurology, Boston, April 25, 1957.

difference greater than 20 decibels between the two ears should not be tested. The distance between the actual source of sound and the spot where the pointer lands is called the angular deflection. It is recorded in degrees in a peripheral visual field chart (figure 2).

RESULTS

The results of the normal series are recorded in table 1.

TABLE 1

Subject		Complete Test	Difference Between L and R	Subject		Complete Test	Difference Between L and R
1	R	7.5	4.3	16	R	6.2	2.0
2	R	7.1	1.2	17	R	5.1	0.5
3	R	7.4	1.2	18	R	6.5	0.4
4	R	5.4	0.0	19	R	10.7	0.2
5	R	8.3	0.1	20	R	8.3	0.4
6	R	5.6	0.8	21	R	5.6	5.4
7	R	8.1	0.3	22	R	7.9	2.5
8	L	12.0	2.0	23	L	7.6	0.2
9	R	6.3	0.6	24	R	9.0	2.2
10	R	9.0	4.7	25	R	6.8	0.4
11	R	10.5	1.8	26	L	7.3	2.6
12	R	8.0	1.1	27	R	6.7	0.0
13	R	7.7	1.3	28	L	4.7	0.1
14	R	13.7	1.5	29	R	8.0	0.6
15	R	10.1	2.5	30	R	4.6	1.2

L or R after the subject numbers indicates whether they are left- or right-handed.
The figures under the complete test column are obtained by adding the angular deflections for the 13 standard positions and dividing the result by 13.
The figures under the difference between the left and right columns are obtained by subtracting the average angular deflection of the most accurate side from the average angular deflection of the less accurate side.

When the findings of the present series and those of the previously reported one are combined, the following are the total averages for normal and abnormal values.

Normal Values		*Abnormal Values*	
Total average 13 positions	7.3	Values above	15.0
Total averages left auditory field	7.5	Values above	15.0
Total averages right auditory field	7.5	Values above	15.0
Difference between left and right fields	1.7	Values above (unless see below)	5.0

A difference of 5 degrees or more between the left and right auditory fields is normal provided the findings satisfied the following criteria: 1) the total test must be normal, 2) both auditory fields must be below 12, and 3) one auditory field must be below 6.

Results of the Abnormal Series

The findings on 50 patients studied are grouped according to the area of the brain involved. An attempt has been made to include lesions involving the different lobes of the cerebrum, the basal ganglia, the internal capsule, the cerebellum, and a miscellaneous group of cases.

FRONTAL LOBE LESIONS

	Total Test	Left Auditory Field	Right Auditory Field	Difference between L and R
1. Left frontal meningioma above superior frontal convolution. Tested before surgery.	5.8	6.0	5.8	0.2
2. Left basal frontal lobe meningioma with papilledema. Tested before surgery.	6.3	5.7	6.3	0.6

3. Right traumatic frontal lobe lesion; paresis of the left upper extremity. Tested three months after injury.	13.4	14.7	12.1	2.6
4. Right prefrontal and frontal lobe glioblastoma; the patient was confused; E.E.G. bifrontal spikes; ventriculogram showed marked shifting of the system to the left.	15.0	9.8	22.5	12.7

FRONTOPARIETAL LESIONS

	Total Test	*Left Auditory Field*	*Right Auditory Field*	*Difference between L and R*
1. Left traumatic frontoparietal lesion. Right hemiparesis and astereognosia. Tested two months after trauma.	5.1	5.3	5.0	0.3
2. Left frontoparietal meningioma. Tested before surgery.	10.1	12.1	9.1	3.0
3. Right frontoparietal astrocytoma. Tested after surgery.	10.5	11.3	10.3	2.0

PARIETAL LOBE LESIONS

	Total Test	*Left Auditory Field*	*Right Auditory Field*	*Difference between L and R*
1. Left parietal astrocytoma; symmetric hearing loss of 20 to 30 decibels for frequencies above 2,000 cycles. Tested after surgery.	11.5	10.0	12.1	2.1
2. Left parietal depressed fracture; right astereognosia.	12.0	11.3	11.4	0.3
3. Left parietal lobe focus by E.E.G.; grand mal seizures. The patient's intelligence was very low.	15.0	14.0	13.3	0.7
4. Left parietal lobe; meningioma. Tested before surgery.	6.5	5.1	7.3	2.2

PARIETO-OCCIPITAL LESIONS

	Total Test	*Left Auditory Field*	*Right Auditory Field*	*Difference between L and R*
1. The left parietal and occipital lobes were resected because of a large astrocytoma. Tested four months afterward.	8.6	6.7	11.0	4.3

OCCIPITAL LOBE LESIONS

	Total Test	*Left Auditory Field*	*Right Auditory Field*	*Difference between L and R*
1. Right traumatic occipital lobe scar due to shrapnel injury. Left homonomus quadrantopsia. Bilateral symmetrical hearing loss of 30 decibels for frequencies above 3,000 cycles.	7.3	8.8	7.2	1.6

TEMPORAL LOBE LESIONS

	Total Test	*Left Auditory Field*	*Right Auditory Field*	*Difference between L and R*
1. Left temporal astrocytoma over the inferior temporal region. Areas 20, 21, and 37. Testing	13.0	11.3	15.5	4.2
after surgery. One week after radiation therapy.	13.0	11.3	15.3	4.0
Three weeks after radiation.	10.0	7.0	13.8	6.8
Five weeks after radiation.	15.4	13.0	18.0	5.0

2. Left temporal lobe focus by E.E.G.; positive schistosoma agglutination test. Possible left temporal schistosoma granuloma.	16.4	11.1	23.6	12.5
Repeated testing.	15.0	8.7	23.3	14.6
3. Subdural hematoma over the right temporal lobe. Tested after surgery.	13.3	7.5	20.5	13.0
4. Right anterior temporal lobectomy to 3 cm. from the temporal tip. Hearing loss of 20 decibels on the left and 10 decibels on the right. Tested four months after surgery.	15.7	19.2	13.0	6.2
After repeated testing.	20.0	28.3	11.7	16.6
5. Right temporal lobe abscess. Hearing loss of 30 decibels on the left and 10 decibels on the right for 2,000 cycles and above. Areas 42, 22, 21. Three weeks after operation.	8.0	10.1	7.5	2.6
Two months afterward.	29.0	44.0	17.5	26.5
Four months afterward.	28.0	40.0	18.0	22.0
6. Right inferior posterior area of the temporal lobe was removed surgically. Areas 20, 21, 37. Tested after one month of radiation therapy for tumor.	17.6	25.0	13.0	12.0
7. Right temporal lobe was surgically removed to 5 cm. posteriorly from the tip. The amygdala was also removed. Tested one year after surgery.	12.4	21.0	5.3	15.7
8. Right temporal lobe focus by E.E.G.; air study revealed slight cortical atrophy over the right temporal lobe.	15.0	19.0	13.8	5.2
9. Right temporal lobe spike focus by E.E.G. Tested before surgery (lobectomy).	10.5	10.3	10.7	0.4
Tested one week after surgery.	6.0	4.7	7.8	3.1
	16.4	20.0	15.0	5.0

TEMPOROPARIETAL LESIONS

	Total Test	*Left Auditory Field*	*Right Auditory Field*	*Difference between L and R*
1. Right temporoparietal subdural hematoma; confusion. Tested before surgery.	22.0	27.5	18.3	9.2
2. Right temporoparietal subdural hematoma. Tested before surgery.	15.5	19.1	12.5	6.6
	16.6	18.0	16.0	2.0
After one week with repetition of the test.	14.0	17.0	12.0	5.0
3. Right temporoparietal subdural hematoma removed one year before testing.	10.0	8.8	13.0	4.2

TEMPORO-OCCIPITAL LESIONS

	Total Test	*Left Auditory Field*	*Right Auditory Field*	*Difference between L and R*
1. Left porencephalic cyst at the temporo-occipital area. Bilateral symmetric hearing loss for frequencies above 2,000 cycles.	8.8	7.1	13.0	5.9

FRONTOPARIETOTEMPORAL LESIONS

	Total Test	*Left Auditory Field*	*Right Auditory Field*	*Difference between L and R*
1. Left middle cerebral thrombosis; aphasia, right hemiplegia, parietal lobe signs. Testing was done one year afterward.	13.3	5.8	20.8	15.0
2. Left middle cerebral thrombosis; aphasia, right hemiparesis, parietal lobe signs. Tested one year afterward.	18.9	12.3	23.3	15.0

3. Left middle cerebral thrombosis; right hemiplegia, aphasia, parietal lobe signs. Tested three weeks afterward.	17.0	11.6	20.1	8.5
4. Left middle cerebral thrombosis; aphasia, right hemiplegia, parietal lobe signs. Tested three weeks afterward.	21.8	7.8	21.0	13.0
After repeated testing, one month.	9.0	8.6	13.3	4.7
5. Left middle cerebral thrombosis; aphasia, right hemiparesis, parietal lobe signs. Tested two months afterward.	17.0	15.0	20.2	5.2
6. Left internal carotid thrombosis, proved by arteriography. Bilateral symmetric hearing loss of 30 to 40 decibels for frequencies above 3,000 cycles. Tested three weeks afterward.	23.0	15.0	28.1	13.1
7. Diffused metastatic lesions from bronchogenic carcinoma. Right hemiplegia, both sensory and motor aphasia, parietal lobe signs.	19.6	11.1	28.1	17.0

BILATERAL HEMISPHERIC LESIONS

1. Bilateral vascular lesions. Aphasia, profound right hemiplegia, left-sided spasticity, and pseudobulbar symptoms.	The patient was unable to localize any positions on the right. Two positions closed to the midline on the left were localized normally.

CEREBELLAR LESIONS

	Total Test	*Left Auditory Field*	*Right Auditory Field*	*Difference between L and R*
1. Left-sided cerebellar cystic astrocytoma; left cerebellar signs.	10.7	11.6	8.8	2.8
2. Midline cerebellar astrocytoma; bilateral signs.	15.7	13.0	15.0	2.0

MISCELLANEOUS LESIONS

	Total Test	*Left Auditory Field*	*Right Auditory Field*	*Difference between L and R*
1. Internal capsule vascular lesions.				
a. Right-sided; left hemiparesis, no sensory loss and no aphasia.	10.4	12.5	8.7	3.8
b. Left capsular lesion; right hemiparesis, no sensory loss, and no aphasia.	10.0	9.7	10.3	0.6
c. Left capsular lesion; right hemiparesis, no sensory loss, no aphasia.	8.8	8.8	9.0	0.2
2. Temporal lobe seizures. E.E.G., focus; negative air study.				
a. Left temporal uncinate seizures.	10.8	10.8	12.0	1.2
b. Right temporal lobe seizures.	9.2	7.7	10.3	2.6
c. Bilateral temporal spike foci.	6.3	6.0	7.0	1.0
d. Temporal lobe seizures with deja vu phenomenon. Hearing loss of 20 to 30 decibels in the right for frequencies above 3,000 cycles.	6.3	8.6	5.0	3.6
3. Grand mal seizures, no focal discharges in E.E.G.	12.0	11.5	13.3	1.8
4. Huntington's chorea, bilateral movements.	15.3	16.6	15.3	1.3
5. Pituitary chromophobe adenoma.	11.4	11.5	11.3	0.2
6. Brainstem lesions				
a. Weber's syndrome. Third nerve palsy on the left and right corticospinal signs.	10.3	11.5	9.2	2.3
b. Multiple sclerosis; fasciculus disorder, bilateral corticospinal tract signs, left cerebellar signs.	12.3	15.6	11.5	4.1

HYSTERIA OR MALINGERING

	Total Test	Left Auditory Field	Right Auditory Field	Difference between L and R
1. Old right subtemporal decompression for pseudotumor cerebri. The patient received several fist blows to her head. Complained of pain over the operative scar which was not injured.	16.0	13.0	20.0	7.0
After her symptoms disappeared, testing was done without suggestions and without attempting to train her to do better.	14.0	16.0	15.0	1.0
2. Hysterical right hemiparesis, right hemianesthesia, right anosmia, and right hearing loss.	7.2	7.0	7.3	0.3

SUMMARY OF 50 CASES

Area Involved	No. of Cases	Normal Test	Abnormal Test	Area Involved	No. of Cases	Normal Test	Abnormal Test
Frontal lobe	4	3	1	Brainstem	2	2	0
Frontoparietal lobe	3	3	0	Basal ganglia	1	0	1
Parietal lobe	4	4	0	Hysteria	2	1	1
Parieto-occipital lobe	1	1	0	Temporal lobe	9	1	8
Occipital lobe	1	1	0	Temporoparietal lobe	3	1	2
Cerebellum	2	1	1	Temporo-occipital lobe	1	0	1
Internal capsule	3	3	0	Frontoparietotemporal lobe	7	0	7
Temporal lobe seizures	4	4	0	Bilateral hemispheric	1	0	1
Grand mal seizures	1	1	0				
Pituitary tumor	1	1	0				

	50 Normal Subjects	10 Left Temporal Lesions	10 Right Temporal Lesions
Average Total Test Range	7.3 (4.6-13.7)	16.9 (8.8-21.8)	16.6 (10.0-29.0)
Average Left Auditory Field Range	7.5 (4.8-13.0)	10.0 (5.8-15.0)	20.2 (18.8-28.3)
Average Right Auditory Field Range	7.5 (3.2-14.5)	21.0 (13.0-28.1)	13.0 (5.3-18.0)
Average Difference between L and R Range	1.7 (0-5.4)	11.0 (4.2-15.0)	7.2 (0.4-26.5)

DISCUSSION

The findings in this report are in agreement with the previously reported series as to the capacity of normal subjects to make an accurate localization of sound coming in a horizontal plane. There was no instance of confusion of laterality in any of the normal subjects tested. The accuracy of the localizing response in the left and right auditory fields was statistically the same. This observation could be interpreted as indicative of lack of cerebral dominance in this function. None of the normal subjects tested had any significant hearing deficits, although in several cases a 10 to 20 decibel loss was present for different frequencies. The latter group of subjects localized sound well within normal range. Subjects with hearing deficits of more than 20 decibels were excluded from the series. In normal subjects with a difference in hearing acuity of more than 20 decibels, an impairment of localization of sound has been observed in the corresponding side of the deficit. Sounds are displaced toward the most sensitive ear.* Bilateral but symmetric hearing loss for different frequencies does not impair the localizing response to any significant extent. In two cases of the patients series there was a bilateral hearing loss of 20 or 30 decibels, and yet the sound localization test was normal.

In one subject of our normal series the difference between the left and right auditory field was above 5 degrees. This particular subject was extremely accurate in the right auditory field. It was considered normal because the findings fulfilled established criteria.

Out of the 21 cases in which the temporal lobes were involved, 19 showed impairment in the localization of sound, predominantly in the

*Unpublished statistical data gathered in connection with sound localization in the presence of hearing deficits.

contralateral field. A case with a subdural hematoma removed from the temporoparietal area a year before the testing performed normally. It could have been predicted because the pressure effect was relieved a year before and no actual destruction of the temporal lobe had occurred at the time of the operation.

Among the non-temporal lobe lesions there were four instances of abnormal sound localization. One case was due to a marked bilateral cerebellar incoordination, another was due to uncontrolled choreiform movements, and a third was most likely due to hysteria or malingering with abnormal localization in the same side of the symptoms. The fourth case was that of a patient with a right frontal and prefrontal lobe glioblastoma in which there was no filling of the right ventricle and marked shifting of the left ventricular system to the left. At operation the right temporal lobe was noted as normal in appearance. Unfortunately no postmortem examination was obtained in this case. The reason for the abnormal localization of sound in the right auditory field is not known. It could have been that the left temporal lobe was compressed against the bony structure, producing a difficulty in localization of sound on the right side.

In two cases of temporal lobe lesions there was difficulty in localization of sound on the ipsilateral side. This impairment was much less than the contralateral one. The exact reason for this finding is not known; however, the fact that in both instances the patients were confused and had difficulty in understanding the test could offer a possible explanation.

One case with bilateral hemispheric lesions of vascular origin had the most profound disturbance of localization of sound. Another patient with a right temporal lobe abscess on two occasions displaced to the right side sounds that were actually coming from the left auditory field. This patient is the first one who ever complained of difficulty in localizing persons talking to him. When he was with a group of unfamiliar persons, he would have to look at the lips to know which person was talking.

Repeated testing, preceded by a demonstration with the patient's eyes open, was carried out in six cases of temporal lobe lesions.

In one instance the localization impairment became worse as radiation therapy progressed. In two cases the patient's accuracy has improved; however, their localization test is still abnormal. In three cases there has been marked improvement in localization, with two of them reverting to normal.

The capacity of some patients for reverting to normal and the failure of others to do so is not yet understood. Further studies and a longer follow-up are necessary.

It is believed that the temporal lobe plays a leading role in the localization of sound. Damage to one temporal lobe fairly consistently produces an impairment of localization of sound in the contralateral auditory field.

Human orientation to a three-dimensional space requires very complicated and involved processes. Of the different sensory channels by which information is obtained and transferred to the central nervous system, the visual system plays, perhaps, the most significant role. Hearing, however, is another means by which awareness of the outside space is obtained. Just as the parietal lobe functions in the localization of touch and the occipitoparietal region in the orientation of objects in space, so should the temporal lobe function in sound localization.

Before this test can be considered a valuable clinical tool, it must meet the judgment of experience and time. However, in the meantime it may be useful in the evaluation of temporal lobe disease and in the investigation of the physiology of sound perception in space.

There are definite limitations to this test, such as marked confusion, pronounced hearing deficits, and conditions that produce uncoordinated or abnormal movements.

SUMMARY

1. The localization of sound in a series of 50 normal subjects is reported.

2. The findings in a series of 50 patients with lesions of different etiologies and sites of involvement are reported.

3. Cases with temporal lobe lesions in most instances manifest impairment of sound localization in the contralateral auditory field.

4. Observations are made as to the apparent function of the temporal lobe in the localization of sound. This function is compared with the localization of touch and with the visual orientation of objects in space.

5. The possibilities and limitations of the sound localization test are mentioned.

The authors wish to express their gratitude to Miss Josephine Adamson, chief librarian of Mt. Alto Veterans Administration Hospital, for her assistance in localizing the references, and to Mr. Victor R. Landi, chief of the medical illustration service, Mt. Alto hospital, for his assistance in the preparation of the illustrations.

REFERENCE

1. Sanchez-Longo, Luis P., Forster, F. M., and Auth, T. L.: A clinical test for sound localization and its applications. Neurology 7:655, 1957.

Dilantin in the Treatment of Trigeminal Neuralgia

Anthony Iannone, M.D., A. B. Baker, M.D. and Frank Morrell, M.D.

SOME EARLY INVESTIGATIONS on frog sciatic nerve[1] and squid giant axon[2] indicated that sodium Dilantin added to the bathing fluid significantly reduced the excitability of nerves rendered hyperexcitable by sodium oxalate. Our own observations on frog nerve[3] confirmed these findings and led us to further experimental studies utilizing mammalian preparations. It was then noted that the "nerve repetitions," or "rebound" spike, induced with constant current stimulation was abolished by systemically administered sodium Dilantin.[4] On the supposition that pain of peripheral nerve origin was related to repetitive discharge in the afferent fiber or end organs, it was decided to investigate the effects of this drug in a group of patients with trigeminal neuralgia.

Parenthetically, it may be noted that Penfield and Dattner, in a discussion of an intriguing paper by Caveness and co-workers,[5] suggested that the paroxysmal features of such syndromes as lancinating pain of neurosyphilis, trigeminal neuralgia, and Menière's disease might reflect a peripheral epileptiform discharge amenable to anticonvulsant therapy. As far as we have been able to discover, however, the suggestion was never investigated in the case of trigeminal neuralgia.

Five patients have been placed on Dilantin since October 1956. It is felt that the results of treatment in these patients have been striking enough to justify a preliminary report.

Case 1. A 62 year old university professor suffered an attack of lancinating pain above the right eye and in the right cheek in 1954. The pain was intermittent in nature and appeared in attacks several times daily. The patient was given injections of vitamin B_{12} and the pain subsided after two weeks. In September 1956 the pains recurred, became much more intense, and occurred three or four times daily, lasting approximately one hour. The attacks could be triggered from the forehead, eyelid, or roof of the mouth. The patient obtained no relief from intramuscular vitamin B_{12} or intravenous procaine. He was admitted to the hospital on October 10, 1957. Neurologic examination was normal, except for areas of hyperesthesia in the forehead, eyelid, and the roof of the mouth. An attack of pain could be reproduced by stimulating these areas. Laboratory and roentgenographic studies were normal. The patient had constant attacks of pain during his first day in the hospital. On the second hospital day, he was placed on Dilantin 0.1 gm. three times daily. By the next morning he felt better and was relatively free of pain. However, he touched off a severe paroxysm of pain when he touched his face with a wash cloth. This paroxysmal attack continued over a 45-minute period. The Dilantin was increased to 0.1 gm. four times daily at this time. By the next day the patient noted that his pain appeared only in short spasms, localized to a small area in the right forehead region, and that the trigger area in the roof of the mouth had improved. The dosage of Dilantin was increased to 0.6 gm. daily, at which time the patient felt only minimal twinges of pain. Within the next two days his pain completely disappeared. At this point the patient began to develop ataxia and nausea. Following this, the dosage of Dilantin was alternately lowered and raised.

The clinical picture at different stages of treatment appeared to be dependent on drug level. On doses of 0.3 gm. Dilantin per day the pain in areas of radiation tended to disappear, although it could be reproduced by stimulation of the trigger area. Pain in the region of the trigger point tended to persist and still caused the patient distress. At 0.4 gm. of Dilantin per day the patient noticed a localization of paresthesia in the region of the trigger point. This was not particularly painful. Raising the dosage above this level produced complete relief of symptoms but with corresponding signs of Dilantin toxicity. Once these effects were noted, lowering the dosage of Dilantin was tried. When this was done the patient's pain came on as originally described, and giving the patient adequate amounts of drug again completely relieved his symptoms. This was done on at least three separate occasions, with reproduction of the clinical attack, followed by relief on administration of the drug. The patient was then discharged on Dilantin 0.4 gm. per day and by February 1957 he was able to cut this down gradually without initiating a paroxysm. He was then able to remain pain-free without medication until April 1957. At that time he again felt some twinges of pain in his right face and immediately resumed Dilantin 0.3 gm. per day. He obtained relief of pain within 24 hours. He remained on this drug for one month and was then able to discontinue it without any recurrence of pain. He has been pain-free since.

From the division of neurology, University of Minnesota Medical School, Minneapolis, Minnesota.
This work was supported by the Teagle Foundation.

Case 2. A 50 year old man first suffered the onset of burning, shooting pain into his left jaw three years previously. The pain was intermittent and persisted for a period of several weeks. There was a recurrence of pain in July 1956. This recurrent episode continued during the next few months, and the patient was finally referred to University Hospital for definitive treatment. Examination was entirely negative, except for the facial pain which could be precipitated by talking or eating. The patient was placed on Dilantin 0.1 gm. three times daily, and experienced complete relief of pain after 24 hours; he was continued on the Dilantin for three weeks. He remained pain-free after discontinuing Dilantin, except for the presence of occasional paresthesias in the right cheek. His remission lasted for ten months, at which time he again developed some paroxysmal facial pain which was promptly relieved by Dilantin 0.1 gm. three times daily. He has been pain-free since.

Case 3. An 82 year old female experienced the onset of pain in the left cheek in 1952. This became more persistent over a two-year period. She continued to have recurrent attacks of pain in the left third division of the trifacial nerve, with a trigger point in the mouth. Her attacks lasted several days and returned every second or third week. She was referred to the hospital for root section. While in the hospital she was placed on Dilantin 0.1 gm. three times daily, and became completely pain-free within 24 hours. She continued medication for approximately two months. Within 72 hours after discontinuing Dilantin her pain recurred, but administration of the drug produced relief within 24 hours. This same procedure was repeated on three separate occasions with the same results. The patient has since remained on Dilantin and has remained pain-free.

Case 4. A 59 year old man first suffered the onset of pain in the right eye and forehead six years previously. These attacks were paroxysmal, radiating into the right eye and right forehead. After approximately six weeks, pain subsided and the patient experienced a recurrence of pain only during each winter. The last episode of pain began in the summer of 1957, affecting the right eye and forehead, with a trigger point in the mouth which kept him from eating. He could precipitate an attack by washing his face. The right supraorbital nerve was injected with alcohol, producing good anesthesia in the distribution of the nerve but no relief of pain. An infraorbital nerve injection was then done with no relief. The pain then improved spontaneously during the next few days, but the patient still noticed paresthesias and burning. He was placed on Dilantin 0.1 gm. three times daily. This medication was continued for one week with no change in the pattern of the pain. The drug was then discontinued by the attending physician. The patient is still having attacks of pain.

Case 5. A 48 year old housewife developed severe attacks of pain in the throat in October 1956. This pain radiated into the neck and right ear, and was initiated in the tonsillar region and aggravated by swallowing. Between attacks the patient had a peculiar feeling in the right throat and transient pain occurred on swallowing cold water. She was started on Dilantin 0.1 gm. three times daily in November 1956 and experienced relief of pain within two days. She remained pain-free, but developed a rash after a few weeks of medication. In addition, she complained of nausea. The dosage was lowered to 0.1 gm. twice daily, but on this dosage she noticed occasional twinges of pain in her throat, usually triggered by drinking cold water. In April 1957 she had a severe attack of pain which was not controlled by cocainizing her throat. Increasing the dosage of Dilantin to 0.1 gm. three times daily relieved her pain within 24 hours. She remained on this dosage through the summer, with occasional stabs of pain in her throat. She experienced another severe episode of pain in September 1957. Her throat was cocainized during this attack with some relief of pain. She was then given 0.2 gm. of Dilantin intravenously; at the end of a half hour she noticed a lessening of the pain so that it became possible for her to swallow oral medication. She still noticed an extremely painful trigger point. She was then given 0.2 gm. of Dilantin and Nembutal 0.2 gm. orally. The patient was able to sleep and was free of pain by the next morning. Since then she has been free of pain on Dilantin 0.1 gm. three times daily.

DISCUSSION

The small number of patients and the short period of observation are both inadequate to permit definite conclusions as to the efficacy and scope of this treatment method.[6] Many more patients must be studied before any but preliminary impressions can be reported.

Our reasons for believing that Dilantin does affect the course in these patients rests primarily on the fact that relief from the drug is reversible, that is, if pain relief occurs on Dilantin, the pain returns if the drug is stopped. This was demonstrated in two different patients on six separate occasions. This reproduction of pain by sudden withdrawal has not been noted in other drugs reportedly effective in trigeminal neuralgia.

Another reason for believing that these effects are specific to Dilantin and are not placebo effects is that relief of pain never occurs immediately after administration, but always approximately 24 hours later. Conversely, when recurrence of pain occurs on drug withdrawal, it does not appear for 48 to 72 hours. This correlates well with known pharmacologic properties of Dilantin. Other drugs, such as nicotinic acid, vitamin B_{12}, and intravenous

procaine have been tried in these patients without demonstrable success.

The pattern of response was worthy of note. The first response was in the areas of radiation of pain, followed by a lessening of pain and excitability in the trigger area. If there is a prompt response to the initial dosage, the pain is usually completely gone by the next day. Persistence of pain in the region of the trigger area is an indication for increasing the dosage of the drug, if necessary, to the point where nausea and ataxia are produced. Our policy at present is to try to keep the patient pain-free for a period of at least one month before discontinuing the drug. Usually the dosage can then be lowered without recurrence of pain, although in one instance (case 3) we have been forced to maintain the patient on Dilantin indefinitely in order to continue pain relief. If a patient has experienced relief with this drug, another attack is usually relieved promptly by restarting Dilantin.

The use of intravenous Dilantin would appear to offer a more rapid method of obtaining relief from paroxysms of pain. To date, our experience is limited to only one patient (case 5), and this does not appear to be any more effective than the oral medication. This will be pursued further in the future.

It should be stressed that the effect of Dilantin appears to be symptomatic. There is no evidence that this drug in any way alters the underlying disease process which is present. For this reason, recurrences of pain after a course of Dilantin should occur at the same frequency as one would expect with no treatment at all. We can only speculate about the nature of this effect and emphasize the possibility that the drug may exert its effect on the membrane properties of peripheral nerve rather than on central synaptic mechanisms.[4]

CONCLUSIONS

1. Dilantin was administered to four patients with trigeminal neuralgia and one patient with glosopharyngeal neuralgia.

2. In all of the patients to whom adequate dosage of Dilantin has been administered, definite relief of the pain was obtained and the paroxysms of pain controlled.

3. It is suggested that Dilantin used orally may prove to be a valuable addition to treatment of painful paroxysmal disorders of the face.

The experimental basis for this work is reported in the paper by Morrell, Bradley, and Ptashne[4] appearing in this issue of NEUROLOGY.

REFERENCES

1. TOMAN, JAMES E. P.: The neuropharmacology of antiepileptics. EEG & Clin. Neurophysiol. 1:33, 1949.
2. KOREY, SAUL R.: Effect of Dilantin and Mesantoin on the giant axon of the squid. Proc. Soc. Exper. Biol. & Med. 76:297, 1951.
3. MORRELL, F.: Unpublished observations.
4. MORRELL, F., BRADLEY, W., and PTASHNE, M.: Effect of diphenylhydantoin on peripheral nerve. Neurology 8:140, 1958.
5. CAVENESS, WILLIAM, ADAMS, RAYMOND D., POPE, ALFRED, and WEGNER, WALTER R.: The role of the dorsal root ganglia in the production of the lancinating pains of central nervous system syphilis. Tr. Am. Neurol. A. 1949, pp. 60-64.
6. RUSHTON, J. G., and MCDONALD, H. N. A.: Trigeminal neuralgia: Special considerations of nonsurgical treatment. J.A.M.A. 165:437, 1957.

■ A section of the olivary bodies is followed, not by any marked degree of paralysis, or anaesthesia, but by a state of persistent spasm in many muscles on the *same* side of the body, in the neck especially — a state which may sometimes continue for days, weeks, or even months. It is found, also, that this strange result is produced by irritating several parts of the base of the encephalon, the lateral and posterior parts of the medulla oblongata and pons Varolii especially, as well as by irritating the olivary bodies. These parts are not very clearly defined.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

A Study on Traumatic Lumbar Punctures

Wallace W. Tourtellotte, Ph.D., M.D., John F. Somers, M.D.,*
Julius A. Parker, A.B., Hideo H. Itabashi, M.D. and
Russell N. DeJong, M.D.

THE USE of anticoagulant therapy in the treatment of cerebrovascular diseases has reopened the problem of differentiating with certainty between vascular accidents of hemorrhagic origin and those secondary to thrombosis or embolism. Since either gross blood or xanthochromia is found in the cerebrospinal fluid of a major percentage of patients with intracerebral hemorrhage,[1-3] a spinal puncture is done to aid in differentiating between hemorrhage and thrombosis before the institution of anticoagulant therapy. A hemorrhagic cerebrospinal fluid on lumbar puncture, however, does not give positive evidence that the blood arose from an intracranial hemorrhage; the possibility of a "traumatic tap" must be eliminated.

Classically there are several methods used to distinguish fluid contaminated with blood produced by the diagnostic needle from bloody fluid secondary to intracranial bleeding. Bleeding from trauma at the time of the puncture may be recognized by the following: 1) The fluid is collected in two or preferably three tubes; each consecutive tube is more clear than the preceding one. 2) Cell counts done on the successive samples show a progressive decrease in erythrocytes. 3) No crenated red blood cells are present. 4) If allowed to stand, the blood may clot, but only when the red blood cell count exceeds 200,000.[3] 5) The supernatant fluid is clear after centrifuging. 6) Repeating the puncture in a higher interspace with clean equipment should yield clear fluid. 7) Repeating the puncture on successive days should show nonpigmented fluid.

According to McMenemy,[3] the most reliable method of distinction is a decrease in the amount of blood in the three tubes as the needle is washed through by spinal fluid. Barrows and co-workers[4] recently studied xanthochromic cerebrospinal fluid by means of a spectrophotometric technic. In seven traumatic punctures they found no hemoglobin or other pigments in the supernatant fluid after centrifuging.

In the present investigation, the reliability of the serial tube analysis to distinguish normal spinal fluid which is contaminated with blood produced by the diagnostic needle is further confirmed by using a spectrophotometric method similar to that recommended by Barrows. Experiments are presented in which a lumbar puncture was done and clear fluid was collected. The lumbar puncture was then purposefully made hemorrhagic and bloody fluid was collected in two or three tubes in series. The collected specimens were stored at room temperature or in an ice bath for various periods of time before quantitative analysis for oxyhemoglobin and/or bilirubin.

METHODS

A standard lumbar puncture was done and clear fluid was obtained in the first tube for routine diagnostic study. The puncture was then made traumatic by advancing the needle until the anterior wall of the spinal canal was encountered. By withdrawing the needle to the center of the canal, hemorrhagic spinal fluid was obtained and collected in a second tube. A third tube was taken one to two milliliters later and, on some occasions, a fourth tube one to two milliliters after this.

The analytic scheme is presented in figure 1. Two hundred μl. of each sample were transferred with a Lang-Levy pipette to a pointed tube measuring 5 by 55 mm. (outside diameter) and centrifuged 20 minutes in a cold room (4° C.) or at room temperature (centrifuge temperatures up to 41° C. have been recorded) at 2,900 r.p.m.

An absorption spectrum was determined on a 60 μl. aliquot of the supernatant by reading in the Beckman model DU spectrophotometer modified to read 50 μl. at 350, 370, 400, 405, 410, 412, 415, 417, 420, 450, 480, 540, 575, and 630 mμ. The filter was in position 2 from 350 to 400 and in position 1 from 405 to 630. The photomultiplier was set at full. The blue sensitive phototube was used with resistor 2 for all wave lengths except 630, for which the red sensitive phototube with resistor 1 was used. The slit width was adjusted at each wave length to give the mini-

From the department of neurology, University Hospital, and neurochemistry laboratory, Kresge Medical Research Building, University of Michigan, Ann Arbor, Michigan.
This work was supported by the Kenneth H. Campbell Foundation for Neurological Research.
*Summer clerkship sponsored by the National Institute of Neurological Diseases and Blindness.

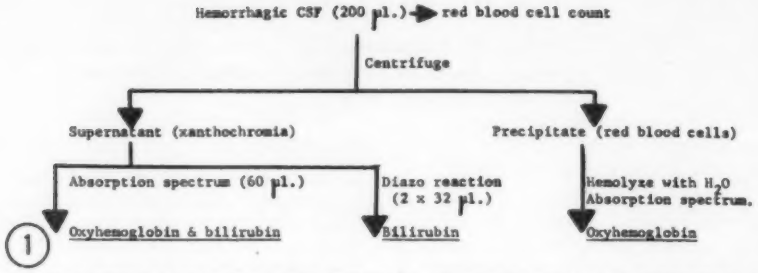


FIG. 1. Flow diagram of the analysis. Three fractions are determined directly: 1) the oxyhemoglobin and bilirubin and 2) the bilirubin alone of the supernatant fluid, and 3) the oxyhemoglobin of the red blood cell precipitate. The oxyhemoglobin of the supernatant fluid is calculated by the method described.

mum band width. The wave lengths selected are the minimum data necessary to characterize the oxyhemoglobin, bilirubin, and methemoglobin in solution. It should be stated that Barrows established that xanthochromia is mainly the result of oxyhemoglobin and/or bilirubin, but rarely methemoglobin. Oxyhemoglobin has a deep absorption band in the 410 to 415 range and less intense peaks of equal magnitude at 540 and 575. Also, there is a sharp fall from 415 to 540. On the other hand, no peak at 412 but a plateau from 430 to 480 with a sharp fall to 540 mμ characterizes bilirubin. A mixture of oxyhemoglobin and bilirubin gives a peak around 412, then a plateau from 430 to 480, with a sharp fall to 540. The 540 mμ, absorption is more intense than that at 575 mμ.

The Malloy-Evelyn serum bilirubin procedure was adapted for spinal fluid in several ways.[5] It was not found necessary to dilute fluid and all the volumes were drastically reduced. All solutions were made up as described by Malloy and Evelyn. Forty μl. of methanol and 8 μl. of fresh diazo reagent are mixed in a small reaction tube (5 by 55 mm. outside dimensions). Thirty-two μl. of spinal fluid are added. The tube is capped with parafilm and gently inverted several times. A blank is prepared as above, except 8 μl. of HCl blank solution replaces the diazo reagent. The blank and the tissue sample are centrifuged for 20 minutes at room temperature at 2,900 r.p.m. after standing for ten minutes to pack any flocculant that might develop. The supernatant is then carefully transferred to a microcuvette and read in the spectrophotometer at 540 mμ. In figure 2 is presented the bilirubin standard curve. The data are linear from 0.05 to 1.0 mg. per 100 ml. The equation of the line is shown on the graph.[6] Y is the optical density times 1,000, minus 14 is the intercept, 361.3 is the slope, and X is milligrams of bilirubin per 100 ml. of fluid. The optic density (times 1,000) of the blank corrected tissue sample is substituted for Y in the equation of the line, and X is calculated.

Oxyhemoglobin and methemoglobin have very similar absorption curves and a molar extinction coefficient that is approximately the same. No attempt has been made in this paper to separate them, and their total absorption is presented in terms of oxyhemoglobin.

The determination of the oxyhemoglobin concentration was based on the deep absorption band at 412 mμ. (The determination based on the 540 mμ. absorption or on the cyanomethemoglobin method was found too insensitive.) The reliability of the procedure was established in several ways. It was first shown that on 21 nonpigmented specimens the average optical density (times 1,000) at 412 mμ. was 16. Furthermore, all spinal fluid specimens tested showed an absorption curve in the visible spectrum, but there was no evidence of any characteristic absorption peaks. An exam-

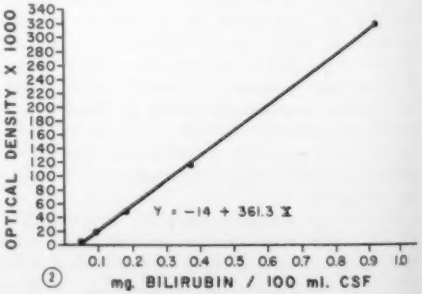


FIG. 2. The bilirubin standard curve.

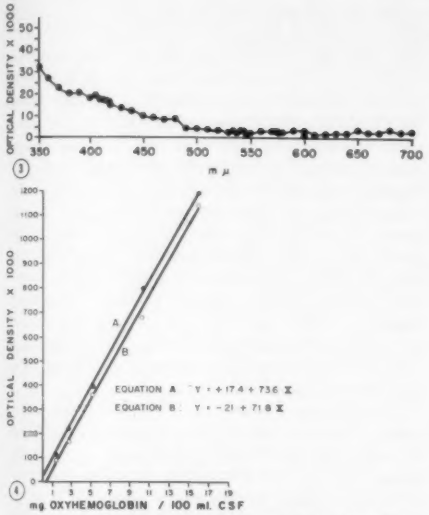


FIG. 3. A spectrophotometric graph of the absorption curve of a spinal fluid specimen which contained no blood pigments.

FIG. 4. The oxyhemoglobin standard curve for the supernatant fluid is shown in *A* and that for the red blood cells hemolyzed in water is shown in *B*. The wave length used was 412 mμ.

ple of the absorption curve of a nonpigmented fluid is shown in figure 3. In figure 4 are shown the direct relationship between optical density and oxyhemoglobin concentration. The data are based on dilutions of an oxyhemoglobin standard (standardized by the cyanomethemoglobin method[7]) ranging from 0.5 to 16 mg. per 100 ml. By inspection it can be seen that there is a straight line function between optical density and hemoglobin concentration, with a significant intercept for both curves. The equations of the lines are given.

The equation A shown in figure 4 for oxyhemoglobin in the supernatant of centrifuged spinal fluid is applicable if the fluid does not contain bilirubin. If the optical density at 412 mμ. is 71 (optical density times 1,000), then by substitution in the equation and solving for X, the oxyhemoglobin concentration is found to be 0.73 mg. per 100 ml. If, however, bilirubin and oxyhemoglobin are both present in the fluid, as is the case several days after a subarachnoid hemorrhage, the optical density at 412 mμ. is the sum of the optical density of each component.[8] The concentration of oxyhemoglobin can be calculated in the following manner. The concentration of bilirubin is determined by the modified Malloy-Evelyn technic previously described. The bilirubin (milligrams per 100 ml.) is converted to the optical density (times 1,000) at 412 mμ. by a nomogram shown in figure 5; this value is then subtracted from the observed 412 mμ. optical density, and the difference is the optical density contributed by the oxyhemoglobin. This optical density is then converted to milligrams per 100 ml. by the use of the equation A shown in figure 4.

The red blood cells suspended in hemorrhagic spinal fluid can be readily quantitated as milligrams of oxyhemoglobin per 100 ml. After centrifugation and aliquots of the supernatant for the diazo reaction and the absorption spectrum are taken, the remainder of the supernatant is carefully removed by aspiration, using great care to avoid disturbing the precipitate. Two hundred μl. of glass double distilled water are added and the tube is shaken. After standing 30 minutes the tube is again shaken and the solution is read in the Beckman spectrophotometer, as described for the supernatant. The optical density (times 1,000) at 412 mμ. is substituted in equation B given in figure 4, and milligrams per 100 ml. are determined. If the optical density is 1,000 or more, a dilution of the hemolysed red cell precipitate has been found necessary. After appropriate dilution corrections are made, the equation B in figure 4 is applicable.

The data in figure 6 show a positive correlation between the observed oxyhemoglobin concentration of laked red blood cells and the calculated oxyhemoglobin concentration expected on the basis of the red blood cell count when it is assumed that each red blood cell contained 30 micro-micrograms of hemoglobin. Therefore, if the oxyhemoglobin concentration due to red blood cells is determined, it is possible to calculate the red blood cell count (divide the hemoglobin concentration by 30 micromicrograms). It has been found that the oxyhemoglobin method is too insensitive to detect 100 red blood cells per cu. mm. when 200 μl. of fluid were centrifuged and the precipitated red blood cells were laked in 200 μl. of distilled water.

STUDIES ON HEMOLYSIS

Barrows and co-workers included in their paper some *in vitro* studies in which sterile suspensions of red blood cells were added to clear spinal fluid. After two hours incubation at 38° C., they found large amounts of oxyhemoglobin in the supernatant, which continued to increase with further incubation. To study hemolysis under the same conditions

except at 4° C., we performed the following experiment. A final concentration of spinal fluid was made with 2,000 red blood cells per cu. mm. Aliquots were centrifuged and examined as described above at intervals from 30 minutes to nine hours. It was interesting to note that there was an increase in the optical density throughout the recorded range (up to 20 per cent of the initial value) without any evidence of specific absorption bands. A further experiment was done in which the preparation was then placed at room temperature (22 to 25° C.) for 15 more hours. Only one per cent of the red blood cells added could have been hemolyzed to give the 412 mμ. absorption which was observed. These preliminary data indicated that insignificant hemolysis developed in hemorrhagic fluid at room temperature or at 4° C.

The effect of temperature and time on the hemolysis of red blood cells in spinal fluid was further investigated by comparing fluid before and after a purposeful traumatic lumbar puncture. The clear and hemorrhagic fluids were then incubated at room temperature and at 4° C. at intervals from 30 minutes to six hours. Eleven such experiments were done. Hemolysis in the supernatant, as shown by the presence of an oxyhemoglobin peak, occurred only in four specimens with large amounts of blood, 6,000 to 123,000 red blood cells per cu. mm. The degree of hemolysis was small (0.5 to 3 per cent of the total red blood cells) and at the temperatures studied there was no increase of the 412 mμ. peak with time. These data may indicate that hemolysis of the "weak" red cells occurred by the time the first specimen was examined (usually 30 minutes) and the majority of red blood cells are quite stable in spinal fluid at these temperatures up to six hours. It should be noted that the most constant effect was a small increase in the optical density throughout the recorded range, without evidence of any pigment peaks. This effect increased with time and was more pronounced in the room temperature tubes. The maximum change was twice the optical density of the nonhemorrhagic fluid.

From these studies then, it has been concluded that storage of hemorrhagic spinal fluid at room temperature for periods up to six hours before centrifuging is probably permissible for evaluation of xanthochromia. To minimize hemolysis, however, it is recommended that a measured amount of mixed hemorrhagic fluid be centrifuged immediately, the supernatant removed and collected into a clean tube, and both tubes stored in the refrigerator at 4° C. until the studies for blood pigments can be carried out.

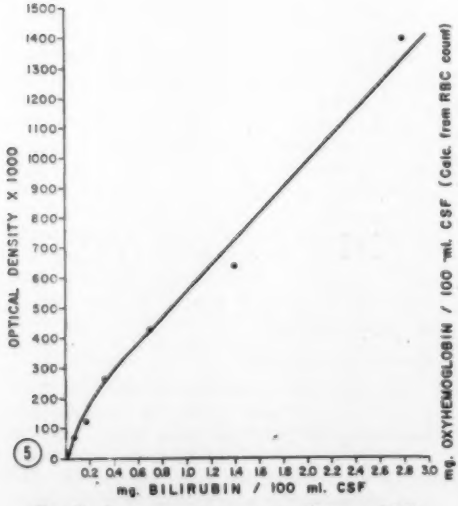


FIG. 5. A nomogram to convert milligrams of bilirubin per 100 ml. of cerebrospinal fluid to optical density (times 1,000) at a wave length of 412 mμ.

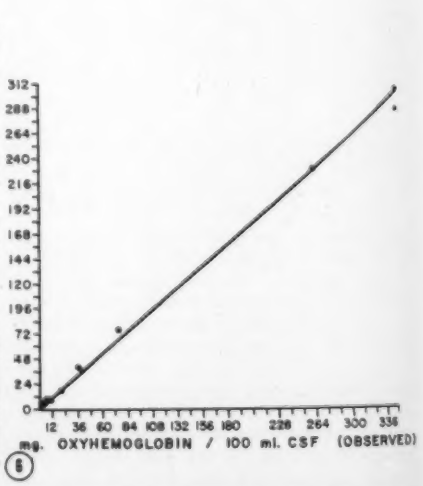


FIG. 6. Correlation between the oxyhemoglobin content (in milligrams per 100 ml. of cerebrospinal fluid) calculated on the basis of the erythrocyte count and that observed by the method described in the text.

RESULTS AND DISCUSSION

In table 1 are presented the oxyhemoglobin concentrations of the supernatant fluid and red blood cells, as well as the red blood cell count in serial spinal fluid samples obtained at purposeful hemorrhagic lumbar punctures on six different patients. The description in column 3 indicates the color change in the serial tubes, as noted by gross inspection. It can be gleaned from the data that a specimen which contains at least 360 red blood cells per cu. mm. can appear perfectly clear. McMenemy has reported 500 as about the limit of visibility recorded in the red blood cell count.[3] It should be noted that in all cases no red blood cells were seen in tube 1, and that after the traumatic lumbar puncture erythrocytes were present in every instance. The third and fourth tubes in all cases showed a marked decrease. To further substantiate this observation, the data in column 5 indicate the oxyhemoglobin concentration in the cells. In column 6 is shown the oxyhemoglobin concentration in the supernatant fluid of the centrifugate. These data indicate that oxyhemoglobin can occur in the supernatant when the lumbar puncture is very hemorrhagic (12,000 red blood cells per cu. mm.). Therefore, its persistence in serial tubes cannot be taken as an indication of a subarachnoid hemorrhage. McMenemy also indicated that a trace of color is seen in the supernatant when the red blood cell contamination is heavy (150,000 to 200,000 cells). However, he expressed the belief that it was due to the serum and not oxyhemoglobin. Our studies indicate that it is due to oxyhemoglobin. We have further shown that it is not due to bilirubin, since the diazo reaction was negative. Also, the spectrophotometric absorption curve did not suggest the presence of bilirubin. (In our hands the absorption curve is more sensitive, but not quantitative.)

It can be seen from the data in table 1 that the fall in either the red blood cell count or the oxyhemoglobin concentration of the red blood cells in the serial tubes is a reliable indication of a traumatic lumbar puncture. Furthermore, when the lumbar puncture is very hemorrhagic (12,000 red blood cells per cu. mm. or more), it has been found that the supernatant fluid of the centrifuged specimen can contain oxyhemoglobin (not bilirubin).

The most important conclusion of this quantitative study is the support given to the classical counting of red blood cells on serial tubes of a hemorrhagic spinal fluid for establishing the presence of a traumatic lumbar puncture. The more complicated, accurate, and reproducible oxyhemoglobin method presented here soundly supports this clinically more readily available but less accurate method.

TABLE 1

(1)	(2)	(3)	(4)	*Observed oxyhemoglobin (mg. per 100 ml.)*	
CSF No.	*Tube No.*	*Gross Description*	*Red blood cells per cu. mm.*	(5) *red blood cells*	(6) *supernatant*
J.M. 872655	1	clear	0	0	0
	2	pink tinge	1,500	4.9	0
	3	clear	90	<0.3	0
	4	clear	10	<0.3	0
M.L. 871271	1	clear	0	0	0
	2	pink tinge	3,360	9.2	0
	3	clear	360	3.6	0
K.M. 873409	1	clear	0	0	0
	2	pink tinge	3,950	8.4	0
	3	pink tinge	2,150	5.6	0
M.S. 302738	1	clear	–	0	0
	2	pink tinge	–	24.2	0
	3	clear	–	0	0
W.B. 866349	1	clear	0	0	0
	2	pink tinge	12,100	38.8	<0.3
	3	pink tinge	1,810	7.0	0
	4	clear	230	0.5	0
A.N. 871494	1	clear	0	0	0
	2	pink tinge	121,000	289.0	1.4
	3	pink tinge	25,300	75.4	0.7
M.L. 871271	1	clear	0	0	0
	2	pink tinge	123,000	308.0	1.5
	3	pink tinge	86,900	232.0	2.0

The description, erythrocyte count, and oxyhemoglobin concentration of the erythrocytes and supernatant fluid on serial cerebrospinal fluid samples obtained at purposeful hemorrhagic lumbar punctures.

A few points should be made about the preparation of the serial tubes of a hemorrhagic spinal fluid for subsequent analysis. Where the fluid is heavily contaminated, the amount of fluid collected in the first tube should be just sufficient for analysis (about 0.5 ml.). As much as is feasible should be collected in the second tube, allowing several milliliters of fluid to wash the needle, thus giving as great a difference as possible between the first and the later tubes. It should be emphasized that the tubes should be dry, free of hemolytic agents (such as detergents), and well shaken before sampling for red blood cell counts or oxyhemoglobin concentration. If the contamination is over 1,000 red blood cells per cu. mm., it is recommended that the fluid be diluted a known amount with red blood cell diluent (dilutions made in a white blood cell pipette have been found satisfactory up to 100,000 cells per cu. mm.).

Xanthochromia may be seen in traumatic lumbar punctures if the contamination is heavy (as demonstrated above) or if the patient has also had a subarachnoid hemorrhage. It is possible in these conditions to establish the presence of a traumatic lumbar puncture by the fact that the red blood cell precipitate decreases from tube one to tube three. If the contamination is very heavy and there is xanthochromia, only a second puncture at a higher interspace or serial lumbar punctures can assess the significance of the hemorrhagic fluid. If the patient has had a subarachnoid hemorrhage a few days prior to puncture, as well as a traumatic lumbar puncture, bilirubin would be present in the fluid.[4] Furthermore, it has been shown that, in contamination of spinal fluid by blood, the total protein is raised 1.5 mg. per 100 ml. for every 1,000 fresh red blood cells per cu. mm.

The quantitative study of hemorrhagic spinal fluid has a number of applications. As illustrated in this report, the diagnosis of a traumatic lumbar puncture can be made. If it can be established that there is no blood in the spinal fluid of a patient who has had a cerebrovascular accident, the clinician is on relatively safe grounds for instituting prolonged anticoagulant therapy. It is reasonable to assume that the quantitation of red blood cells and blood pigments in the fluid of a patient who has sustained a subarachnoid hemorrhage will be of value in assessing the severity of and recovery from the hemorrhage. For example, serial examinations can establish quantitatively the rate of change of the blood and its derivatives and offer to the clinician a measured way, other than the clinical observation, of evaluating the activity of the source of the hemorrhage.

SUMMARY

1. Methods for estimating blood pigments (oxyhemoglobin and bilirubin) and the oxyhemoglobin of the red blood cells in hemorrhagic cerebrospinal fluid have been studied. The technics are described.

2. It has been shown that insignificant hemolysis developed in hemorrhagic spinal fluid at room temperature and even less at 4° C. up to six hours. The most hemolysis was seen when the red blood cell contamination was heaviest.

3. A spinal fluid which contains 360 red blood cells per cu. mm. appears grossly clear.

4. It has been shown on purposeful traumatic lumbar punctures that the fall in red blood cell count or the oxyhemoglobin concentration of the red blood cells in the serial tubes is a reliable indication of a traumatic lumbar puncture. Furthermore, when the lumbar puncture is very hemorrhagic (12,000 red blood cells per cu. mm. or more), it has been found that the supernatant fluid of the centrifuged specimen can contain oxyhemoglobin.

REFERENCES

1. Walton, J. N.: Subarachnoid Haemorrhage. Edinburgh, E. & S. Livingstone Ltd., 1956.
2. Merritt, H. H.: A Textbook of Neurology. Philadelphia, Lea and Febiger, 1955, p. 171.
3. McMenemy, W. H.: The significance of subarachnoid bleeding. Proc. Roy. Soc. Med. 47:701, 1954.
4. Barrows, L. J., Hunter, F. T., and Banker, B. Q.: The nature and clinical significance of pigments in the cerebrospinal fluid. Brain 78:59, 1955.
5. Malloy, H. T., and Evelyn, K. A.: The determination of bilirubin with the photoelectric colorimeter. J. Biol. Chem. 119:481, 1937.
6. Arkin, H., and Colton, R. R.: Statistical Methods. New York, Barnes and Noble, Inc., 1956.
7. Crosby, W. H., Munn, J. I., and Furth, F. W.: Standardizing a method for clinical hemoglobinometry. U.S. Armed Forces Med. J. 5:693, 1954.
8. Hunter, F. T.: The Quantitation of Mixtures of Hemoglobin Derivatives by Photoelectric Spectrophotometry. Springfield, Illinois, Charles C Thomas, 1951.

Caudate Lesions and Spontaneous Locomotion in the Monkey

George D. Davis, Ph.D.

One of the best known sequelae of frontal lobe damage is the development of restlessness in the human or locomotor hyperactivity in the monkey and lower animals. Brickner,[1] Rylander,[2] and Freeman and Watts[3] have commented on the excessive ambulation of many patients following prefrontal lobotomy. In addition, animal experiments since the days of Ferrier[4] have repeatedly demonstrated this cause-effect relationship.

Attempts at localization of the exact frontal lobe structures involved in this phenomenon have been much less consistent. Only a few of the studies on activity and the frontal lobes have involved measurement of the amount of locomotion of the animals. The majority have relied on visual observations. The first series which involved objective and quantitative recordings was that of Richter and Hines,[5] who concluded that activity was increased by lesions of area 9 and of the striatum. Kennard, Spencer, and Fountain[6] implicated areas 8, 9, 10, 11, and 12 and specifically denied any contribution of the corpus striatum in the production of locomotor hyperactivity. Ruch and Shenkin,[7] also measuring the amount of ambulation in their monkeys, produced great activity changes with lesions of area 13 on the orbital surface.

Mettler,[8] using visual observations only, considered that "over-reactivity" follows general frontal cortical lesions, while "overactivity" was thought to result from "removal of area 9 alone or, more particularly, striatal damage." Turner[9] has used measurements of activity in a study involving stereotaxic lesions of the caudate nucleus, and, although the records might have been taken in a more precise fashion, a definite relationship between striatum and hyperactivity appears.

Recently, Rosvold and Delgado[10] have published a study reporting the effects of stimulation and electrocoagulation with electrodes implanted in the caudate nucleus and putamen. They reported that visually observed activity increases following either stimulation or destruction in putamen and after destruction of the caudate nucleus.

The present study was undertaken with a very sensitive test apparatus which does not interfere in any respect with a monkey's spontaneous activity and which allows measurement of a wider spectrum of locomotion than any test cage previously employed in such studies. One of the prime objectives of this work is to demonstrate that hyperactivity is not the "all-or-none" phenomenon that some previous workers have considered it, but is instead a major derangement of a rather nicely balanced innate activity level. With small lesions and accurate testing, it is possible to demonstrate the fine control which exists in this mechanism.

Experimental Procedure

Rhesus monkeys (Macaca mulatta) were used in this study. The majority of the animals were immature upon arrival. Approximately half of these matured at some time during the postoperative observation period. A few of the animals were mature before operation. Maturity has not proved to be a factor either in activity or operative effects in this study.

All lesions were made with the use of a Johnson stereotaxic instrument and insulated nichrome electrode. Lesions were produced with 90 volts, 3 milliamperes current, applied for 45 seconds. The lesions were of a remarkably uniform size and shape. When multiple lesions were made, at least 90 seconds were allowed to elapse between current applications. This insured adequate cooling of surrounding tissue.

Activity was recorded in two test cages. The basic test cage has been described previously.[11] Basically it records one count for each cage crossing of approximately four feet by means of a photo-cell system. Activity is also permitted on perches above the floor of this test cage. Standard tests are run in this cage for two or three hours per day on each animal before operation on at least six occasions, or until a satisfactorily steady level of activity is recorded. The animals are then tested from

From the department of physiology, Louisiana State University School of Medicine, New Orleans, Louisiana.
Aided by a grant (B-874) from the National Institutes of Health, U. S. Public Health Service.
Read at the ninth annual meeting of the American Academy of Neurology, Boston, April 27, 1957.

the first postoperative day onward until a full evaluation of locomotion change can be obtained. The animals do not receive food until they have finished the activity test of the day. Temperature, light, and sound in the testing room are carefully controlled and the animals are tested in total isolation. The animals are trained to transfer through carrying cages to the test situation with a minimum of disturbance.

The second activity cage is similar in operation and size to the basic test situation. This cage, however, has been especially fitted for observations of 24 hours or longer. Hour-by-hour activity recording and light-dark cycles in this cage are totally automatic. Feeding is done once a day at a regular time and the influence of long-term factors on activity can be studied in this way. Agreement of results between the two cages has been excellent.

Following activity, neurologic observation, and such other testing as is indicated, the animals are sacrificed with saline followed by formalin perfusion. The brains are sectioned at 25 micra and selected sections are stained for study of the lesion and for elimination of the possibility of any other type of injury to the brain. Drawings of the lesions are carefully made for comparison with the activity results.

RESULTS

Activity from unilateral lesions. In six out of seven cases of unilateral lesions of the caudate nucleus, activity increases of from two to five times were seen. Two examples of this operation are seen in animals *A.S. 1* and *A.S. 11* in figure 1. In *A.S. 1* the center of the lesion is somewhat posterior to that seen in *A.S. 11*. The more anterior placement (caudate head) has seemed to produce a somewhat greater increase in ambulation in animals in this series. The percentage activity change in these two monkeys was approximately equal, even though the lesion of *A.S. 1* involved a considerably larger volume of nucleus. The laterality of the lesions made no visible difference in the effects on locomotion. Circling as a definite entity was not seen in any of these animals. At least two of the animals with unilateral lesions preferred to pace in a figure 8 pattern, as demonstrated by closed-circuit television observation of the monkeys in the test situation. This effectively eliminates the possibility of turning preference following such lesions. In general the animals tended to follow the same type of activity pattern postoperatively they had exhibited before operation.

The most marked alteration in such patterns was a tendency to spend more of their time on the floor of the cage and less on the upper bars. However, the activity increase was generalized and not restricted completely to an increased floor pacing.

Activity from bilateral lesions. When bilateral lesions of the caudate nucleus were made either at one operation or by a subsequent operation on an animal already having a unilateral lesion, the results did not differ in either magnitude nor type of activity. In figure 1 animals *A.S. 8* and *A.S. 9* received the two stage operation, while the lesions in *A.S. 16* were made simultaneously. It should be noted that *A.S. 8* eventually became four times as active as *A.S. 9* after each had lost nearly equal amounts of caudate tissue, but it must also be clear that *A.S. 8* was ten times more active before any surgery. *A.S. 16* is illustrative of the great magnitude of locomotion increase which can be obtained with large lesions involving both caudate and putamen but entirely without direct cortical destruction. Activity increase appeared to correlate with volume of striatal tissue destroyed in all cases. The increased locomotion following a simultaneous bilateral lesion was almost exactly equal to the total activity increase achieved by two unilateral lesions of the same size spaced one month apart. It is also interesting to note that the activity increase was about the same whether the lesion in the caudate was made by multiple lesions placed in a single coronal plane or multiple lesions placed in a single sagittal plane.

Latency of activity increase. In a previous series involving cranioplasties with subpial resections, it was noted that the hyperactivity was very minimal if the animals were tested three or four days postoperatively, while, if the first test came more than a week after operation, the hyperactivity was frequently as well established as it would be subsequently. This latency has been mentioned in several other studies of activity changes. Because of the minimal surgical trauma involved in this procedure, tests were made routinely on the first and subsequent postoperative days. It was found that hyperactivity following lesions of the caudate nucleus is fully established in about seven days. On the first postoperative day activity is unchanged from control level. This is not a result of postoperative physical conditions, since animals already quite hyperactive because of a large unilateral lesion exhibit this degree of hyperactivity on the day

following a second lesion. Subsequent tests show a gradual increase of locomotion until the activity stabilizes between the seventh and tenth postoperative days. This amount of activity is then seen on all subsequent tests for as long as a year and a half.

A second phenomenon which may have some connection with the latency of onset of hyperactivity has been seen in two monkeys with large unilateral lesions and one animal with large bilateral lesions. For seven to ten days all activity was observed on the upper bars of the test cage. Prior to operation about two-thirds of the normal activity had been on the floor. This locomotion started at the control preoperative level and increased until total activity at the end of the period was as high as any subsequently recorded – yet this locomotion was entirely above the floor of the cage. On the ninth or tenth postoperative day a gradual shift to floor activity began and, within two weeks from the date of operation, the majority of the hyperactivity was occurring as pacing on the floor.

Neurologic observations. All the animals in this study were subjected to careful neurologic examination before and after each lesion. In none of the animals were any motor or sensory deficits or aberrations detected. Observers agreed that these animals were in no way remarkable neurologically. The only non-locomotor abnormality ever observed was seen in the same group of three animals with large lesions just discussed. All three animals of this group exhibited a behavior during the period of upper bar activity which we have termed "forced placing." This was particularly evident in the transit cage which consists of a small box, the front of which is traversed by a series of horizontal bars. When in this cage, these animals would grasp various of the bars with either or both hands in rapid succession, continuing this behavior for long periods. Similar activity was also seen in the living and test cages, but for much shorter periods. It is surmised that this "forced placing" may have been a substitute for the locomotor hyperactivity which was impossible in the small transit cage.

Longterm tests. Observations carried out on the same animals in the second test cage have confirmed the constant and permanent nature of the activity increases following striatal damage. The effects of varying the lighting in this cage have been evaluated. Under the standard conditions of illumination from 6 a.m. to 6 p.m., activity starts promptly when the light comes on, is maintained for 12 hours, and ceases as soon as the light is extinguished.

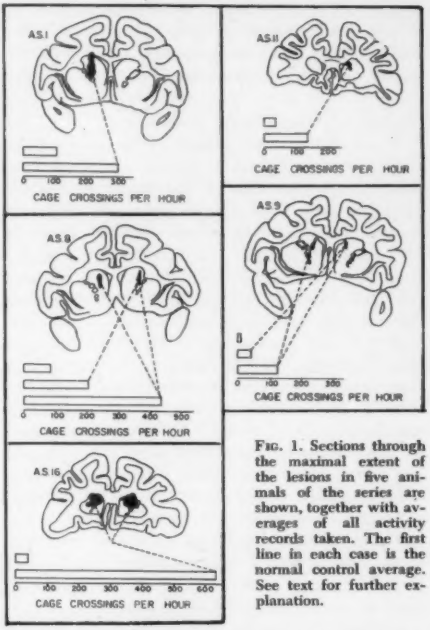


FIG. 1. Sections through the maximal extent of the lesions in five animals of the series are shown, together with averages of all activity records taken. The first line in each case is the normal control average. See text for further explanation.

However, if the light is kept on for 24 hours, activity is drastically diminished during the normal "night" period. Similarly, if the light is not on for a 24-hour period, there is a limited amount of activity during what would ordinarily be the "daytime." This effect is seen in both normal and operated animals. In neither case is the locomotion in darkness comparable to that recorded with the standard illumination schedule. The operated animal tested in 24 hours of darkness is still significantly more active than the unoperated monkey.

DISCUSSION

The data obtained in this study appeared sufficient to implicate the caudate nucleus in the phenomenon of locomotor hyperactivity. All of the animals with bilateral caudate lesions showed a degree of activity increase commensurate with the size of the lesion, and all but one of the animals with unilateral lesions showed such an increase. The only explanation which can be presently offered to explain the absence of effect in this animal concerns the histologic appearance of the lesion. The lesion in this case was a single electrolized focus.

Upon examination most of the boundaries of this lesion showed a clear demarkation between areas of normal nuclear cells and the lesion area which contained no cells of any sort. In this case there was virtually a total absence of tissue injury reaction.

In all of the other lesions of the series there were varying degrees of gliosis, and in several cases the entire area of the lesion was occupied by such products of injury reaction. It is still too early to state whether there is or is not an irritative aspect to the production of locomotor hyperactivity. As yet, we have not obtained satisfactory information concerning the individual contribution of the putamen in the production of increased locomotion. Rosvold and Delgado have stated that they saw the greatest hyperactivity in monkeys with lesions of the putamen. While several of our largest caudate injuries have encroached on the putamen, the activity increase obtained has been compatible with what would have been expected if the same volume of caudate cells had been destroyed. Small lesions of the putamen, similar to those shown in the caudate, have proved disappointing so far. A larger series is now in progress, designed to resolve the putamen's role in activity.

Further discussion is also required of the terminology used in this and other studies. It must be recognized that, of the animals reported in the figure, only *A.S. 16* can be definitely termed "hyperactive." *A.S. 1* and *A.S. 8*, in addition to *A.S. 16*, showed the "bouts of pacing" said to be typical of the hyperactive animal. Viewed in another light, however, it can readily be seen that, while the activity of *A.S. 8* was increased five times by the two lesions, the spontaneous locomotion of *A.S. 9* became 15 times as great following essentially similar injuries. Thus, it is felt that careful establishment of the normal activity of these monkeys is of great importance. *A.S. 9*, after two caudate lesions, crossed the test cage about twice each minute. This certainly does not appear to be hyperactivity until one recognizes that, on a long series of tests before operation, this same animal crossed on the average once every eight minutes and never oftener than once every five minutes. Only an incredibly patient visual observer could possibly have detected the striking change in this monkey.

The matter of latency of activity increase following damage to the caudate nucleus is also unresolved. It is possible that this too is brought about by cellular reaction to electrolytic injury. Equally plausible in the light of current theories of the function of the nervous system is the suggestion that this represents a chemical or metabolic alteration requiring some period of time for its completion. One must consider the fact that hyperactivity, once established, persists to a uniform degree for the remainder of the animal's life, even though this is two or more years. Thus, the latency of the appearance of hyperactivity is inexorably linked with the unanswered question of the exact genesis of hyperactivity itself.

The "forced placing" represents a second type of well coordinated motor hyperactivity. The rapid, sequential hand placing is also observed in normal monkeys and monkeys with long existing lesions of the caudate nucleus when under the influence of such central excitant drugs as amphetamine and phenidylate. As has been pointed out in a previous paper, both of these drugs diminish drastically the amount of locomotor hyperactivity.

No symptoms of the gastrointestinal difficulties reported by Rosvold and Delgado[10] were seen in any of the monkeys in this series, even following large simultaneous bilateral lesions of caudate and putamen. There was never any retching or vomiting at any time in the postoperative period. The appetite of the animals was good at all times, but they were never hyperphagic. Weight gain through postoperative periods as long as two years was completely normal when compared with unoperated animals over the same length of time.

It is believed that this study provides further proof for the theory that major caudate injury alone can lead to the phenomenon of locomotor hyperactivity. It must be recognized that evidence is as yet insufficient to state that cortical injury without striatal involvement cannot also lead to increased locomotor activity. Considerable further work is now in progress in the hope that a clearcut answer to the putamen and cortical roles in activity can be obtained.

SUMMARY

1. Small lesions of the caudate nucleus have produced locomotor activity increases in monkeys, the extent of the increase showing a good correlation with the volume of tissue damage.

2. Unilateral and bilateral lesions are effective in increasing activity and no "forced circling" is seen following a unilateral injury of either side.

3. A behavior designated as "forced plac-

ing" is seen in monkeys with large caudate lesions immediately after operation, especially when locomotion is restricted.

4. Monkeys with large caudate lesions pass through an "arboreal" phase during the period of activity increase, which later gives rise to the floor pacing previously reported.

5. Hyperactivity is reduced but not eliminated by darkness during normal waking hours and is also reduced if light is continued during normal times of sleep.

The author wishes to express his appreciation to Mr. Joseph August for his technical assistance in all phases of this study.

REFERENCES

1. Brickner, R. M.: The Intellectual Functions of the Frontal Lobes. New York, Macmillan, 1936.
2. Rylander, G.: Personality Changes after Operations on the Frontal Lobes. Copenhagen, Einar Munksgaard, 1939.
3. Freeman, W., and Watts, J. W.: Psychosurgery. Intelligence, Emotion and Social Behavior Following Prefrontal Lobotomy for Mental Disorders. Springfield, Illinois, Charles C Thomas, 1942.
4. Ferrier, D.: The Function of the Brain. London, Smith Elder & Co., 1876.
5. Richter, C. P., and Hines, M.: Increased spontaneous activity produced in monkeys by brain lesions. Brain 61:1, 1938.
6. Kennard, M. A., Spencer, S., and Fountain, G. Jr.: Hyperactivity in monkeys following lesions of the frontal lobes. J. Neurophysiol. 4:512, 1941.
7. Ruch, T. C., and Shenkin, H. A.: The relation of area 13 on orbital surface of frontal lobes to hyperactivity and hyperphagia in monkeys. J. Neurophysiol. 6:349, 1943.
8. Mettler, F. A.: The experimental anatomophysiologic approach to the study of diseases of the basal ganglia. J. Neuropath. & Exper. Neurol. 14:115, 1955.
9. Turner, E. A.: Cerebral control of respiration. Brain 77:448, 1954.
10. Rosvold, H. E., and Delgado, J. M. R.: The effect on delayed-alternation test performance of stimulating or destroying electrically structures within the frontal lobes of the monkey's brain. J. Comp. & Physiol. Psychol. 49:365, 1956.
11. Davis, G. D.: Effects of central excitant and depressant drugs on locomotor activity in the monkey. Am. J. Physiol. 188:619, 1957.

■ Some learned men have thought that the persons represented in the sacred writings as possessed by demons, were epileptics. The circumstances of one case in particular are pointed out as perfectly well agreeing with those of epilepsy. — A youth is said to have been subject to attacks, in which he uttered loud cries, and fell to the ground, or into the fire or the water, being so agitated and torn by an unclean spirit, as to gnash with his teeth, and foam at the mouth. During these seizures, he is said to have been possessed by a dumb and deaf spirit. This has been understood to mean, that in the paroxysms of the disease, he was dumb and deaf. The departure of the spirit from him spoken of, has been supposed to denote the interval between the fits. It has been observed, that the miracles wrought on the demoniacs are often described by the same terms as those used to express the miraculous restoration of persons stated to have been *diseased*. It is said equally of demoniacs, lunatics, and paralytics, he *healed* them. The daughter of the woman of Canaan, who was grievously vexed with a demon was *cured*, or as it is translated, made whole.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Effect of Diphenylhydantion on Peripheral Nerve

Frank Morrell, M.D., William Bradley, M.D. and Mark Ptashne

A NUMBER of previous investigations[1,2] have indicated that sodium Dilantin alters the properties of peripheral nerve when the latter is subjected to unusual or unphysiologic stimulating conditions. These studies have, for the most part, employed non-mammalian nerves, excised and placed in moist chambers where the nerve could be bathed in various concentrations of the drug.

The observations to be reported here are concerned with mammalian peripheral nerve, recorded *in situ*, under more or less physiologic conditions of stimulation.

METHOD

A total of 48 rabbits weighing between 2 and 3.5 kg. were used for this study. Under light Nembutal anesthesia, the posterior tibial nerve was exposed and dissected free for 2 or 3 cm. of its length. The nerve was suspended on two platinum wire electrodes 3 mm. apart which were insulated in plastic except at the point of contact with the nerve. The electrode assembly was placed between the surrounding muscles so that the nerve was not stretched and was in contact with interstitial fluid. Leads were connected to the input of a differential push-pull amplifier and the amplified potentials viewed through a cathode ray oscillograph, the sweep of which was triggered by the stimulating pulse. Monophasic square-wave pulses were provided by a Grass stimulator and isolation unit and were conveyed to the animal via steel needle electrodes inserted into the foot pad. This method, rather than direct stimulation of the nerve, was employed so that possible variations in end-organ responsiveness might also be observed. Distance between stimulating and recording electrodes was 7 to 8 cm. Care was taken to preserve the blood supply to the nerve and to maintain body temperature between 34° and 37° C. The sodium salt of Dilantin, as the clinical product, was administered intravenously or intraperitoneally so that the nerve was perfused via its own arterial supply. In several experiments, after the observations on one nerve were completed, the contralateral nerve was dissected free and stimulated. This served as another safeguard against possible effects of exposure or drying.

RESULTS

Although a wide variety of forms and duration of stimuli have been studied under these conditions, there are only two basic parameters of stimulation pertinent to this report. Rectangular shocks with a duration of 0.1 msec. will be referred to as "short duration" stimuli. The term "long duration" stimulus will refer to the passage of a current lasting 10 msec. but otherwise having the same characteristics as the briefer shocks.

Long duration currents such as these are considerably longer than the shock-response time. It is, of course, unnecessary to use prolonged currents to elicit a simple action potential from the nerve. However, real physiologic stimulation is rarely in terms of less-than-a-millisecond impulses. Under normal circumstances the afferent terminal is subjected to continuous, constant, or graded liberation of energy, which is then somehow translated by the responding fiber into discrete pulsatile units. It was thought that perhaps changes might be found in the neural substrate of the "translation" function.

Corresponding to these two forms of stimulation there are two basic types of response with which we are concerned. Figure 1A illustrates the response to short duration stimulation at three times the threshold voltage. Two potentials are observed: an initial triphasic deflection and a long latency diphasic and often polyphasic action potential.

Figure 1B indicates the response to long duration constant current. Closure of the circuit starts the sweep and the small deflection just before the second group of potentials represents the opening of the circuit. In contrast to the fairly simple response seen in A, a distinct double action potential appears after the cathode closing and again following the cessation of current flow. The latter response is

From the division of neurology, University of Minnesota Medical School, Minneapolis, Minnesota.
This work was supported in part by grants from the graduate faculty of the University of Minnesota, the Teagle Foundation, and from the USPHS, (B1185).

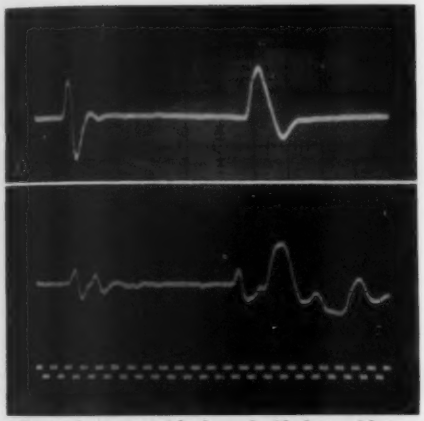


FIG. 1. Action potentials observed with short and long duration stimuli. *A*. 0.1 msec. stimulus, 3 x threshold. *B*. 10 msec. stimulus, 2 x threshold. Time: 1000cy/sec. Temp. 37° C.

mixed with and partially occluded by a polyphasic series of deflections occurring at the same latency as the long-latency potential observed in response to short duration currents.

Since these conditions of stimulation and recording are somewhat unusual in experimental studies, it was important to verify the nature of the potentials before conclusions could be drawn from induced changes in them.

A step by step analysis indicated that the initial deflection represented the synchronized discharge of fast conducting myelinated *A* fibers. The constant latency of 1.5 msec. accords well with the usually assigned conduction velocity of 65 to 69 meters per second for rabbit *A* fibers. The second potential has a considerably more variable latency, ranging from 11 to 14 msec., with a mean of 13 msec. Such a latency might be accounted for by the assumption that this is an efferent volley reflexly elicited from the cord.

The testing of some of these assumptions is indicated in the next figure (figure 2). Tetanic stimulation (A, B, C) reveals that the short latency or initial deflection always maintains a one-for-one response to the stimulus. But at 40/sec. (A) the long latency potential only responds to the first stimulus of the train and then is compeltely wiped out. At 10/sec. (B) it persists but at variable amplitude and latency, and at 2/sec. (C) it shows signs of

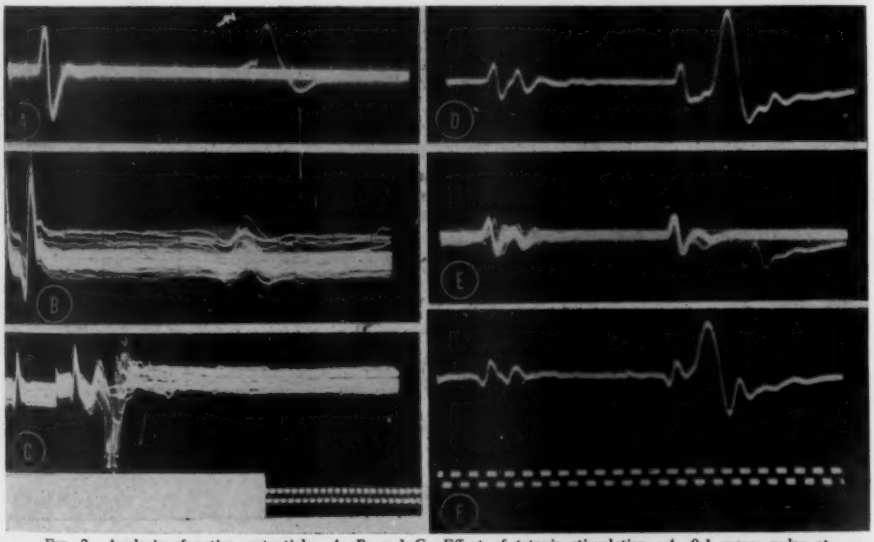


FIG. 2. Analysis of action potentials. *A*, *B*, and *C*—Effect of tetanic stimulation. *A*. 0.1 msec. pulse at 40/sec. (40 consecutive sweeps). *B*. 0.1 msec. pulse at 10/sec. (20 consecutive sweeps). *C*. 7.5 msec. pulse at 2/sec. (10 consecutive sweeps). *D* and *E*—Effect of 40/sec. tetanus on "rebound" spike. *D*. Control. Single stimulus, 10 msec. duration. *E*. 10 msec. pulse at 40/sec. Note disappearance of reflex volley and prominence of the double action potential both at the "on" and the "off" of current. *F*. Effect of increasing conduction distance. Conduction distance in *D* and *E* is 8 cm.; in *F*, 12 cm. Note no separation of crests of the double action potential and a decrease in latency of reflex volley. 10 msec. stimulating pulse. Time: 1000 cy/sec. Temp. 37° C.

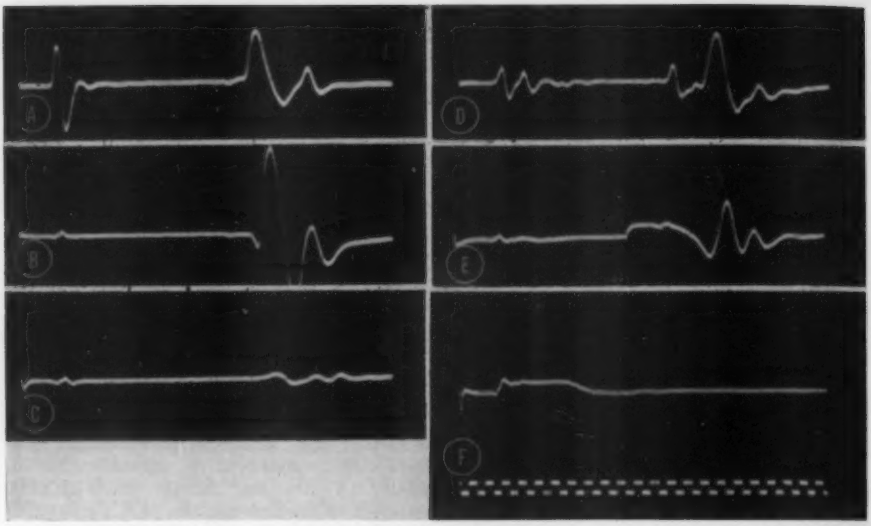


FIG. 3. Effect of Dilantin. *A, B,* and *C*—Short duration stimulation. 0.1 msec. pulse at 3:5 x threshold voltage. *A.* Effect of single shock before Dilantin. *B.* 15 min. after intravenous Dilantin 10 mg./kg. *C.* One hour later. *D* and *E*—Long duration stimulation. 10 msec. pulse at 3 x threshold voltage. *D.* Control. *E.* One hour after intravenous Dilantin 10 mg./kg. *F.* Section of proximal end of nerve abolishes reflex volley. Single stimulus, 0.1 msec. in duration at 3 x threshold voltage, 90 minutes after administration of Dilantin and immediately after nerve section. Time: 1000 cy/sec. Temp. 38° C.

progressive facilitation. Frequency dependent variations such as this strongly suggest the interposition of at least one and perhaps several synapses.

It was noted above that long duration constant currents produced a double action potential or so-called rebound spike both at the onset of current flow and at the cessation of current flow. The latter response was obscured by the superimposition of the long latency reflex volley. Since a 40/sec. tetanus will abolish the reflex volley, this could be employed to demonstrate the second double action potential. Figure 2D is the control response to long duration current; figure 2E is the same response at a 40/sec. tetanus. The reflex volley is abolished and the double action potential both at the "on" and at the "off" of stimulation is thrown into relief.

Analysis of the "rebound" or double action potential included increasing the conduction distance between stimulating and recording electrodes from 8 to 12 cm. If the two peaks represent depolarization of the same fibers and therefore have the same conduction velocity, increasing the distance traveled should produce no separation of the peaks. However, if the second spike represents the depolarization of more slowly conducting elements, then increasing conduction distance should widen the gap between crest-times. Figure 2F indicates that no such separation of peaks takes place. Of further interest is that the latency of the long-latency potential is decreased rather than increased—further indication that it is an efferent rather than an afferent potential.

Finally, of course, (figure 3F) the nerve was sectioned proximal to the recording electrodes and the long-latency response thereby abolished. Since the nerve section in this instance was done after the effect of intravenous Dilantin had been exerted and the effect is not altered, one may conclude that the site of action is peripheral and does not depend on alteration of antidromic or efferent conductive systems to the end organs.[3]

EFFECT OF DILANTIN

Figure 3 illustrates the effect of intravenous administration of 10 to 15 mg./kg. of sodium Dilantin. In A, B, and C single stimulation at 0.1 msec. pulse duration is employed. A is the control response. B is 15 minutes after Dilantin. Threshold has doubled and the same supramaximal stimulus as in A produces a barely visible A fiber action potential and at

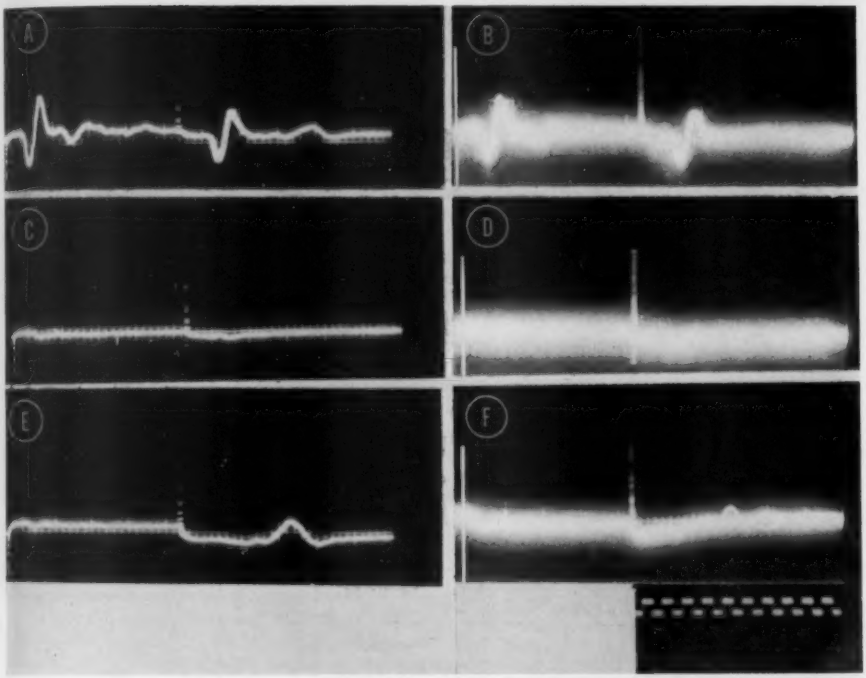


FIG. 4. Effect of Dilantin on oxalated nerve. Explanation of technic in text. *A*. Previously subthreshold stimulus (10 msec. duration) elicits prominent action potential after nerve has soaked in sodium oxalate for one hour. *C*. Response to the same voltage applied one hour after intravenous Dilantin 10 mg./kg. *E*. Voltage increased 10 x elicits reflex volley but negligible change in primary A fiber potential. *B*, *D*, and *F* indicate the same observations utilizing a 40/sec. tetanus. Time: 1000 cy/sec. Temp. 38° C.

the same time a marked amplitude augmentation of the reflex volley together with a prolongation of its latency. The facilitation of the reflex volley is transient, however, and is not seen with intraperitoneal administration of the drug. At one hour it has completely disappeared (figure 3C) and the response latency is further prolonged.

In D and E the stimulating current is applied for 10 msec. D is the control sweep. E indicates the change produced by intravenous Dilantin one hour after administration. Again the threshold had increased two-fold, the spike amplitude of the A fiber potential is markedly decreased, and the second spike of the "double" action potential is abolished. In this animal the reflex volley was changed very little in amplitude (under conditions of long duration stimulation) but was definitely increased in latency.

If the nerve is enclosed in a polyethylene tubing and soaked in sodium oxalate for one or two hours, a drop in threshold occurs to about half the control value. A previously subthreshold shock 10 msec. in duration will then elicit the double action potential spike seen in figure 4A. One hour after intravenous Dilantin the same shock produces a barely visible action potential without the second or "rebound" spike (figure 4C). Increasing the stimulus voltage tenfold (figure 4E) elicits the reflex volley but produces a negligible alteration in the primary A fiber potential. Figure 4B, D, and F are the corresponding observations on a 40/sec. tetanus (40 superimposed sweeps).

In summary, our results indicate that systemically administered diphenylhydantoin produces:

1. An increase of the threshold of peripheral nerve to electrical stimulation of end-organs or nerve endings.

2. A diminution in spike amplitude even to supramaximal stimulation.

3. With intravenous administration, a transient phase of increased central excitation.

4. A prolongation of synaptic delay and/or conduction time.

5. A reversal of the enhanced excitability of oxalated nerve.

6. Abolition of the "rebound" spike induced by long duration currents.

DISCUSSION

Repetitive action potentials in response to supramaximal or long duration currents have been observed previously[1,4] and have been described as Pfluger's and Ritter's "tetanus".[5] The second or "rebound" spike occurs in frog nerve, 3 to 6 msec. and in mammalian nerve, 1 to 2 msec. after the initial compound action potential, and represents a synchronized firing of a large fraction of the A fiber group which had initially responded to the supramaximal stimulating voltage. The phenomenon presumably depends upon rapid accommodation, causing a high degree of supernormality in the recovery period. An overshoot of membrane voltage occurs which is sufficient to cause a second depolarization.

The present findings in mammalian nerve are in contrast to those of Toman[1] and to our own observations[6] on excised frog nerve, and are similar to those of Korey[2] in that not only the "rebound" or repetitive spike but also the primary A fiber action potential was diminished. This would suggest an alteration of the spike generating characteristics of the nerve membrane rather than, or in addition to, an alteration of accommodating properties.

Finally it must be re-emphasized that these alterations were produced in barbitalized animals and that some of the effect may reflect a synergy between the two agents.

SUMMARY

A method of stimulating and recording from mammalian peripheral nerve *in situ* is described. Differences in response to long and short current durations are analyzed, and the effect of sodium Dilantin on nerve action potentials illustrated. Results indicated that Dilantin increased threshold, decreased spike amplitude in A fibers, abolished "nerve repetition," and reversed the enhanced excitability of oxalated nerve. Some speculation as to mechanism is presented.

We would like to express our appreciation to Dr. James E. P. Toman and to Professor Otto Schmitt for helpful discussion and criticism.

REFERENCES

1. Toman, J. E. P.: The neuropharmacology of antiepileptics. EEG & Clin. Neurophysiol. 1:33, 1949.
2. Korey, S. R.: Effect of Dilantin and Mesantoin on the giant axon of the squid. Proc. Soc. Exper. Biol. & Med. 76:297, 1951.
3. List, C. F., and Williams, J. R.: Pathogenesis of trigeminal neuralgia. Arch. Neurol. & Psychiat. 77: 36, 1957.
4. Erlanger, J., and Blair, E. A.: Observations on repetitive responses in axons. Am. J. Physiol. 114:328, 1935/1936.
5. Erlanger, J., and Gasser, H. S.: Electrical Signs of Nervous Activity. Philadelphia, Univ. of Pennsylvania Press. 1937, pp. 103-104.
6. Morrell, F.: Unpublished observations.

■ Tetanus is unhappily no rare or unfamiliar malady. The name, from the Greek "I stretch," refers to that rigid and cramped condition of the muscles which is the most characteristic symptom, and which, in sober earnest, is suggestive of rigor mortis, not only *in posse* but actually *in esse;* for there are some cases in which, without any interval of relaxation, tetanic rigidity at once passes into cadaveric rigidity. Hydrophobia alone excepted, tetanus is at once the most appalling and the most perilous of all spasmodic diseases.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves,* published in 1871.

Occlusion of the Basilar Artery

A Clinical and Pathologic Study of 14 Autopsied Cases

Humberto Cravioto, M.D., J. Rey-Bellet, M.D., Philip H. Prose, M.D. and Irwin Feigin, M.D.

Occlusion of the basilar artery, first described in 1842,[1] has aroused great interest in recent years. Its frequency has come to be recognized since the report of Kubik and Adams,[2] and the possibility of its prevention and treatment has been suggested by Millikan and Siekert.[3] Reports of large series of such cases are few in number.[2,4–6]

The present report deals with 14 autopsied cases of basilar artery occlusion. The clinical, pathogenetic, and pathologic features are reviewed. Attention is given to the cause of occlusion, type of infarct, influence of systemic factors, role of collateral circulation, and the presence in some patients of "coma vigil." In two of these cases the occlusion, complete in one and almost complete in the other, had occurred many months prior to death.

CASE MATERIAL

The material, in part, was gathered from the files of the neuropathology laboratory of Bellevue Hospital and covers the period from January 1938 to October 1956. Infarcts of the brain were observed in 399 of the 4,834 consecutive autopsies which included examination of the brain, an incidence of 8.2 per cent. Of these 399 autopsies, 58 revealed infarcts of the brainstem (sometimes associated with infarcts in other areas of the brain), an incidence of 14.5 per cent of all cases with cerebral infarcts or an incidence of 1.2 per cent of all autopsies. There were 11 cases (0.2 per cent of all autopsies) of complete occlusion of the basilar artery. Of these 11 cases, two were not included in the studies which follow, because of insufficient clinical data. However, we have included five additional cases of occlusion of the basilar artery from other sources; three cases are from the Mount Sinai Hospital, one from the University Hospital-Bellevue Medical Center, and one from the Veterans Administration Hospital, New York City.

HISTORY AND CLINICAL FINDINGS

Of the 14 cases reported here, there were 11 males and three females ranging from 46 to 76 years old, with a median age between 55 and 56 years.

Antecedent heart disease was present in seven patients, in four of whom this was associated with hypertension. A history of antecedent "strokes" at least one year prior to the terminal illness was obtained in two patients, these being patients with heart disease. As will be shown, pathologic examination revealed that the "strokes" in one of these patients were apparently related to occlusion of the basilar artery. Seven patients had neither history of antecedent heart disease nor of arterial hypertension. However, one of these patients had a recent thrombosis of the right brachial artery and another had intermittent claudication of the lower extremities.

There were antecedent symptoms whose relationship to the basilar artery disease was difficult to evaluate; for example, intermittent headache of ten months' duration in one patient, an episode of dizziness one year prior to admission in one patient, brief periods of unconsciousness on several occasions during the two years prior to admission in one patient, a brief period of unconsciousness on one occasion approximately one year prior to admission in one patient, and frequent episodes of vertigo during several months prior to admission in another patient.

Mode of onset. At the time of admission to the hospital one patient was in deep coma. Three patients were in "coma vigil;" they

From the departments of pathology and neurology, New York University-Bellevue Medical Center, New York City.
Read at the ninth annual meeting of the American Academy of Neurology, Boston, April 27, 1957.
This study was supported in part by a grant from the Albert and Mary Lasker Foundation and by grant H2872 of the National Heart Institute of the United States Public Health Service, and forms a part of a study of cerebral vascular disease at Bellevue Hospital by the Cornell-New York University study group on cerebral vascular diseases.

seemed to be aware of their surroundings, since they were able to follow the examiners with their open eyes or they opened and closed their eyes on command. Four patients were in light coma. The latter seven patients had experienced headache, dizziness, slurred speech, vomiting, weakness of the extremities, and visual disturbances, usually blurred vision, during the six to 12 hours before admission.

Six patients were alert and conscious when admitted to the hospital. Four of these had no evidence of organic mental syndrome, one revealed slight mental confusion, and the other was anarthric but alert and able to follow commands. Two of these six patients had transient hemiparesis for four and 24 hours, respectively, and one of these also had dysarthria. One patient had headache, vomiting, dizzy spells, increasing weakness of the right side of the face, the right leg, and left arm, progressive dimness of vision, and dysarthria during the week prior to admission. Another patient had headache, nausea, vomiting, dizziness, dysphagia, numbness of the face, and visual disturbances ("saw things upside down") for a few hours before admission. The fifth patient had frequent episodes of headache, blurred vision, vertigo, and tinnitus during the two weeks prior to admission, and immediately before entering the hospital he experienced a "black-out" lasting for a few seconds. The sixth patient had several episodes of dizziness and dysarthria during the 24 hours before admission, each lasting approximately 15 minutes.

Physical examination. In one of these 14 patients one optic disk was atrophied. No visual field defects were demonstrated. Abnormal movements of the eyes were noted in eight patients: disconjugate gaze was present in six, roving eye movements and nystagmus in one, and nystagmus alone in the other. Pupillary abnormalities in varying combinations were observed in eight cases. These included myosis in seven, irregularity in two, inequality in two, nonreactivity to light in one, and a sluggish reaction to light in two. The corneal reflexes were absent in two patients, one in deep coma and the other alert, and decreased unilaterally in two others. The seventh cranial nerve was involved in seven cases, bilaterally in one and unilaterally in the others. The facial palsy was reported to involve either the lower portion of the face or the type was not specified. Dysarthria was noted in three patients and anarthria in four. The uvula was deviated from the midline in two cases and the tongue protruded abnormally in two others.

In 13 cases there were disturbances of motor power and/or muscular tone. Flaccid hemiparesis was noted in five patients, with involvement of the face on the ipsilateral side in two and the contralateral side in one. Spastic hemiparesis was observed in one patient in whom the face was uninvolved. Quadriparesis was seen in five patients; it was flaccid in four and spastic in one. In these five patients the face was involved bilaterally in one, unilaterally in three, and uninvolved in the other. Two patients had spells of decerebrate rigidity. No motor abnormalities were discerned on admission in the fourteenth patient, although these developed subsequently.

No sensory abnormalities were detected in six patients. Two patients did not react to painful stimuli; one of them was in deep coma and the other was in "coma vigil." One patient had a crossed sensory defect. Irregular sensory defects which involved one, two, or three extremities were observed in five patients.

Nine patients had increased deep tendon reflexes, this being generalized in three, unilateral in five, and limited to one extremity in the other. These reflexes were normal in the other five patients in our series. In seven cases a Babinski toe sign was elicited, bilaterally in five and unilaterally in the other two. The Hoffmann sign was present in three cases; it was bilateral in two and unilateral in the other. Bilateral ankle and patellar clonus was observed in one case.

Arterial hypertension (diastolic pressure above 100 mg. Hg) was recorded in this hospital in three patients and was reported to have been present prior to admission in a fourth.

Course. Seven of the eight patients who were in coma at the time of admission to the hospital continued in the same state, and the other, originally in light coma, subsequently went into "coma vigil." Three patients who were conscious on admission developed progression of symptoms and signs and became comatose within a few hours to ten days. One patient with hemiparesis, dysarthria, nystagmus, and pupillary inequality recovered completely in approximately four hours and remained well for 18 days, but he died while straining at stool. Another patient who was confused and had a left hemiparesis recovered completely within 24 hours of onset, except for slightly increased deep tendon reflexes on

the left side; a month later he suddenly began to sweat profusely and died approximately two hours later. Another patient complained of dizziness, severe dysarthria, drooling, facial weakness, and coldness of the right shoulder and right arm; these findings disappeared in approximately 15 minutes and he remained well for eight hours. These symptoms then recurred episodically for approximately 24 hours; after one of these episodes, the dysarthria persisted and a left hemiparesis and a bilateral Babinski sign became apparent. A few hours later he became stuporous and soon after went into "coma vigil."

Although eight patients entered the hospital with abnormal eye movements, three additional patients showed these abnormalities while in the hospital. In five of these 11 patients both eyes became fixed in the midposition and in two others one eye was so fixed; this fixation could not be altered by sudden passive movement of the head (negative oculocephalic reflex) or by irrigation of the external auditory canal with cold water. When only one eye remained fixed, the other moved in either the lateral or vertical plane. The other four patients showed complete disorganization of eye movements or nystagmus. Abnormal eye movements were not observed in three patients. However, two of these patients died rather suddenly and this may have precluded such observations. In most cases the pupils became unequal or pinpoint in size and fixed to light. Facial weakness was noted on admission in seven patients, in one of whom it was only transient. Facial weakness subsequently became apparent in two others. Of the nine cases with facial weakness, the involvement was bilateral in three.

Irrigation of the external auditory canals with cold water (ear caloric tests) was performed in four patients and abnormal responses were elicited in all cases, with no movement of the eyes, tonic deviation of one eye with nystagmus, or nystagmus of one eye.

The motor system deficits fluctuated in some patients. There was shifting of paresis from spastic to flaccid, or vice versa, shifting of paresis from one side to the other, and temporary improvement followed by exacerbation. Five patients were quadriparetic on entering the hospital and remained so; two other patients became quadriparetic while in the hospital, usually a short time before death. A disorganized changing pattern of muscular tone and deep tendon reflexes was noted in some of the patients. Inconstant fragments of decerebrate rigidity were also observed occasionally.

Hyperthermia as high as 107° F. was recorded in 12 of the 14 patients, usually beginning two or three days prior to death. One patient developed generalized and focal convulsions. Respiratory infections were noted in some patients. The blood pressure remained stable until shortly before death. Diaphoresis was a common finding.

In all cases, death occurred 2.5 to 30 days after admission to the hospital, although one patient had had two prior admissions because of "stroke" 12 and six months prior to death, these being related to the basilar artery occlusion.

Laboratory data. Lumbar puncture was performed in 11 patients. The spinal fluid contained erythrocytes in three cases, 6,840 per cu. mm. in one, 20 per cu. mm. in another, and 15 per cu. mm. in the third. The protein content was elevated in three other instances, 65, 70, and 90 mg. per cent, respectively. In one other patient the initial pressure of the cerebrospinal fluid was 250 mm. H_2O. The Wassermann reaction in the spinal fluid was negative in all cases and this was true of the blood as well.

Skull roentgenograms and other ancillary procedures were not contributory.

Clinical diagnosis. The clinical diagnosis was basilar artery thrombosis in six instances, pontine hemorrhage in one, infarct of the brainstem in another, intracerebral hemorrhage in two, and cerebrovascular accident of unspecified type in four.

PATHOLOGY

Arteriosclerosis of the basilar artery with large atheromatous deposits and marked narrowing of the lumen was present in eight cases. In another case severe arteriosclerotic changes were present in the proximal portion of one posterior cerebral artery, but such changes were only slight in the basilar artery. In the remaining five cases the basilar artery was minimally sclerotic and in only one of these was the lumen somewhat narrowed.

In five of the eight cases with severe arteriosclerosis of the basilar artery, there was evidence of intimal hemorrhage, recent ulceration of an atheromatous plaque, and rupture of the atheromatous material into the lumen; the latter was completely occluded (figure 1). In two other instances the occlusion appeared quite old and entirely consistent with the clinical history of basilar artery occlusion 12 to 18

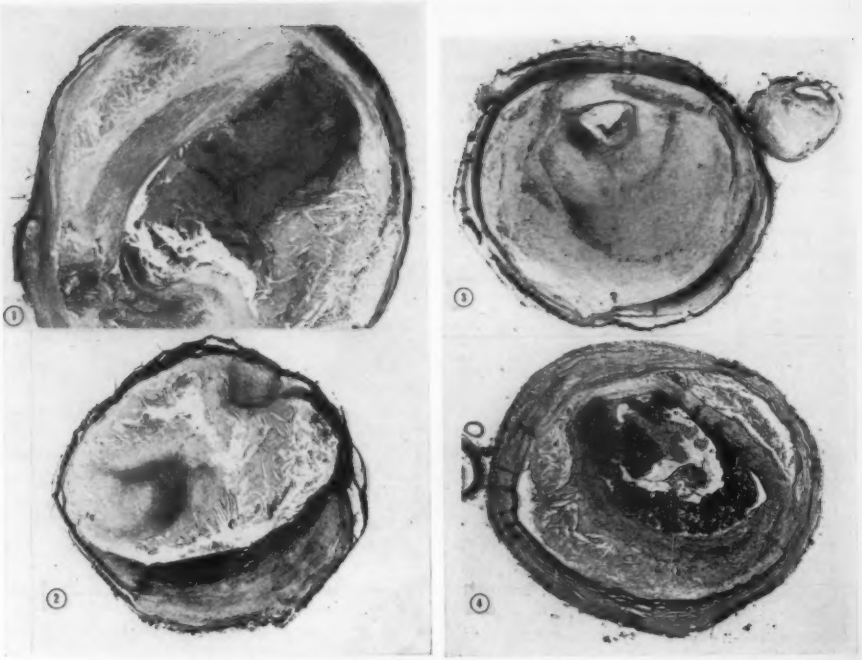


FIG. 1. Basilar artery with large atheromatous plaque within which hemorrhage had occurred. The plaque has ulcerated into the lumen inducing the formation of a thrombus (hematoxylin and eosin stain).

FIG. 2. Basilar artery with eccentrically-placed lumen completely occluded by poorly cellular connective tissue which lies within a large atheromatous plaque (elastic Van Gieson stain).

FIG. 3. Basilar artery with eccentrically-placed lumen markedly narrowed by large arteriosclerotic plaques (hematoxylin and eosin stain).

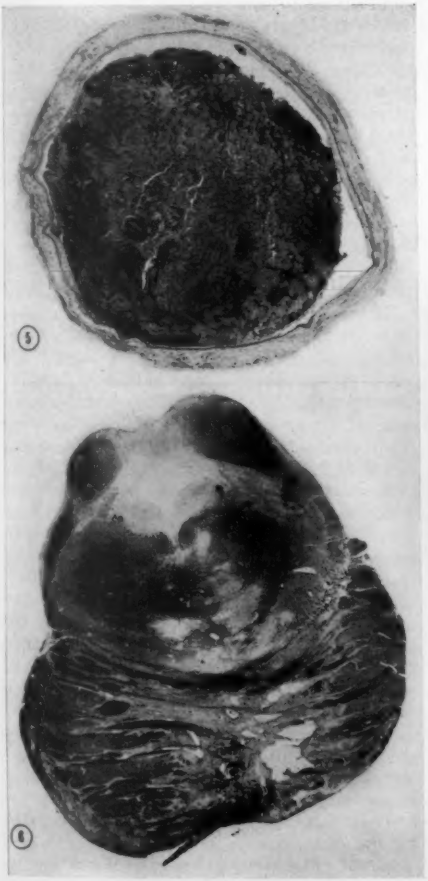
months prior to death. In one of these the lumen was completely occluded by dense, poorly cellular connective tissue which occupied an eccentric position within a large atheromatous plaque (figure 2). In the other, a lumen approximately 0.6 by 0.5 mm. in size at its narrowest point (figure 3) persisted. In this latter case a more recent organizing mural thrombus was present in an adjacent area partially occluding the lumen (figure 4). The basilar artery was only slightly sclerotic in a ninth case, but there was a large atheromatous plaque at the origin of one posterior cerebral artery, upon which an old thrombus was attached and from which a more recent thrombus had extended into the basilar artery and occluded it.

In the other five cases the degree of sclerosis of the basilar artery was slight or minimal. In one of these, an old organized thrombus was present at the bifurcation and did not appear to be attached directly to the vessel wall; a fresh thrombus was also present attached to both the wall and the older thrombus. This patient had had rheumatic mitral stenosis with auricular fibrillation, an infarct in the kidney, and multiple infarcts in the brain, so that an embolic character of the basilar lesion is strongly suggested. In a second case a fresh thrombus of the basilar artery was attached to the vessel wall, which showed minimal sclerotic changes but did show a moderate number of polymorphonuclear leukocytes in the intima. Although a source for emboli was not apparent, the cerebral infarcts were multiple and infarcts were present in the spleen and kidney, and the possibility of embolism is suggested here, as well (figure 5). In the other three cases no infarcts were observed in other organs and no source of emboli was found. In one of these, a thrombus with early organization was

present in the basilar artery and was apparently not attached to the wall; although transient cerebral symptoms had been present a month earlier, no pathologic changes which could account for this episode were observed. Death occurred two hours after the sudden onset of a profound disturbance and no infarct was recognized in any portion of the brain. In this case also, the occlusion may be embolic. In the other two cases the thrombus was organized and attached to the wall and its age appeared to be in accordance with the duration of the clinical features and the age of the infarct.

Infarcts in the brainstem were noted in 12 of the 14 cases of basilar artery occlusion. In all instances, all or portions of the infarcted zones were of recent origin, but in three cases there were in addition small focal lesions which appeared to be quite old (figure 6). The infarct generally involved the base of the pons at various levels, usually the midpons, and was always bilateral, though not symmetrically so (figure 7). There was a tendency for the lateral rim of the base of the pons to be spared (figure 8). The tegmentum of the pons was infarcted almost completely in three cases, slightly in six, and spared in the others. The lower midbrain was involved in nine cases, and this involvement was extensive in four of these. The medulla was involved in only one instance.

In four of the 12 cases with infarcts in the brainstem, the degree of hemorrhage throughout the infarct studied grossly and microscopically was of appreciable degree, so that these lesions may be considered "hemorrhagic"



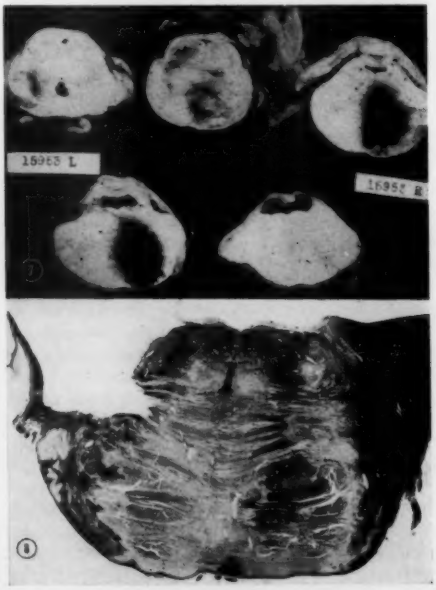


FIG. 5. Basilar artery with minimal arteriosclerosis and an embolus in its lumen (Masson's trichrome stain).

FIG. 6. Upper pons containing old and fresh infarcts in both the base and the tegmentum (Mahon stain for myelin).

FIG. 7. Composite photograph of serial sections of brainstem showing the distribution of recent infarcts.

FIG. 8. Midpons with extensive infarct of the base and part of the tegmentum (We.. stain for myelin).

infarcts. In six cases the infarcted zones were rather pale grossly and contained a few or no red cells microscopically, and these may be considered "anemic" in character. In the other two cases the brainstem revealed both "hemorrhagic" and "anemic" infarcts.

Recent infarcts in one or both occipital and inferior temporal areas were noted in six cases and in the cerebellum in four cases. In two, there were, in addition, old infarcts in the distribution of the carotid system.

Changes in other organs of the body were not relevant, except for the fact that in nine instances the heart weighed more than 400 grams in the absence of valvular disease; arteriolar nephrosclerosis was present in two of these cases and in three others.

DISCUSSION

The incidence of basilar artery occlusion in this series of autopsied cases (approximately 2.3 per thousand), its preponderance in the male (11 of 14 cases), and the age incidence (46 to 76 years, with a median of 55 or 56 years) are quite similar to those recorded by others.[2,4–6] Arteriosclerosis is certainly the most important etiologic factor. In nine cases the thrombus in the basilar artery was considered to be the result of the presence of large atheromatous plaques. In five of these cases intimal hemorrhage and ulceration were readily demonstrable as the inciting mechanism, as has been noted by other observers.[7] In two of the cases in which embolism was thought to be the pathogenetic factor, arteriosclerosis did not involve the basilar artery appreciably, but presumably played a role by involving the coronary arteries, with subsequent myocardial infarction, myocardial fibrosis, and mural thrombosis, although the mural thrombosis was not specifically recognized. The other case thought to be embolic in nature was that of a patient with rheumatic heart disease, mitral stenosis, and auricular fibrillation. The pathogenetic mechanisms in the other two cases with minimal arteriosclerotic involvement of the basilar artery are not clear. The preponderant significance of arteriosclerosis in this condition has been noted by others.[2,6] The incidence of embolism in basilar artery occlusion has been reported as greater than in our series.[2] Additional etiologic factors which have been described in occlusion of the basilar artery include arteritis,[8] aneurysm,[1,5,9] syphilis,[6,10] polycythemia vera with thrombosis,[6] and surgical ligation.[10,11]

Hypertension appears to play a significant role,[4,6] possibly by increasing the severity of arteriosclerotic processes. In 12 of the 14 cases in our series either arteriolar nephrosclerosis was observed or the heart was clearly hypertrophied in the absence of valvular disease, the weight being above 400 grams. In only four of these cases was clinical hypertension observed in this hospital.

In two instances no infarct was noted in the brainstem nor indeed in any other portion of the brain. One of these was the individual who died two hours after the onset of profound symptoms and was thought to have had an embolus. The other was found dead in the bathroom and, at autopsy, a fresh thrombus arising upon a large atheromatous plaque was observed, within which hemorrhage and ulceration had occurred. In these cases it is assumed that death occurred so rapidly that sufficient time had not elapsed for the morphologic changes associated with infarction to have developed. It is to be noted that each of these individuals had had transient neurologic symptoms or signs 18 to 30 days earlier and was still in the hospital, though much improved, at the time of the terminal episode. The observation that infarcts of the brain are not found when the basilar artery is occluded a short time before death is in agreement with similar observations noted after ligation of the basilar artery during surgery.[10]

Pontine infarcts were noted in the other 12 cases. Portions of the infarcted tissues contained considerable hemorrhage in six of these, while in six others hemorrhage was not evident grossly. This variation was also true of infarcts in the cerebellum and in the cerebrum, some being "hemorrhagic" and others "anemic." Three cases thought to be embolic did not differ significantly in this regard; one had no infarct, another a "hemorrhagic" infarct, and in the third there were areas which were "hemorrhagic" and infarcts which were "anemic."

The high incidence of infarction in the brainstem in basilar artery occlusion was not paralleled in the cerebellum or in the inferior temporal and occipital areas of the cerebrum, which are generally supplied by branches of the basilar artery. Infarcts of the occipital and inferior temporal areas were present in only six cases and of the cerebellum in only four. It is evident that a rich collateral circulation exists with respect to these latter sites. In the case of the occipital lobe, a patent posterior communicating vessel is presumably adequate in most cases to maintain the integrity

of these tissues. The cerebellum is supplied by three major branches. If the thrombus within the basilar artery lies between their points of origin, each of these vessels could be supplied from either the vertebral or carotid systems, depending upon the location of the occlusion. When the origin of these branches is occluded by the thrombus, these vessels are presumably rendered inadequate to supply the neural tissues, although there may well be communications among the various cerebellar arteries which tend to bypass such obstruction. Thus, it is clear that the distribution of infarcted tissue in cases of basilar artery occlusion may be quite varied,[12] depending upon the patency of the communicating vessels, particularly the posterior communicating arteries, and on the site of occlusion with respect to the origin of the branches.[10,13–16]

The effectiveness of these anastomotic connections is possibly best demonstrated in the two instances in which the lesion in the basilar artery appeared to be old. In one case the basilar artery was completely occluded by an old organized thrombus. Small, focal, old lesions were present in the brainstem and there was a descending degeneration of the pyramidal tract to the spinal cord. On clinical and pathologic grounds, it is believed that the occlusion had occurred approximately 12 months prior to death. In addition to the old brainstem lesion, fresh lesions were noted in the occipital area, cerebellum, and in the brainstem, and, on clinical and pathologic grounds, these new lesions were approximately one week old. The posterior communicating arteries in this case were very small, estimated to be less than 0.3 mm. in diameter. A very significant fact is the maintenance of the integrity of the tissues in the occipitotemporal areas and, to a large degree, the brainstem for a period of at least one year, in spite of a complete obstruction of the basilar artery and very narrow posterior communicating vessels. It would appear that there were rich anastomotic connections between the cerebral arteries which permitted the block in the basilar artery to be circumvented, despite the narrow posterior communicating vessels. As previously noted by others,[10,15,17,18] there are rich communications between the middle and posterior cerebral arteries and among the long cerebellar vessels.[19,20] Another point of interest is the terminal event, in which these anastomotic connections proved inadequate and large infarcts developed in the affected tissues. Since there is no morphologic evidence of recent change in any of the vessels related to these areas, we may assume that the infarcts were the result of systemic effects, such as a drop in effective blood pressure, which further and critically decreased the blood flow to areas with little or no reserve capacity above the minimum required.[21–23]

In a second instance a somewhat similar situation prevailed, in that the posterior communicating arteries were very small in a patient in whom the basilar artery was almost completely occluded by an old sclerotic plaque which had left only a minute lumen estimated to be approximately 0.6 mm. in diameter. Old and recent infarcts were observed in the brainstem. In addition, at other levels in an adjacent location in the basilar artery there was an organizing mural thrombus which did not further narrow the lumen. On clinical and pathologic grounds, the sclerotic plaque in the basilar artery was estimated to be at least one year old, and we might surmise that the terminal infarction was the result of systemic factors and, less likely, the mural thrombus. The influence of the latter must be evaluated in the light of the fact that the narrowest point in the lumen was at the site of the old sclerotic plaque, not at the site of the mural thrombus.

Four of these cases demonstrated that bizarre clinical syndrome which has been termed "coma vigil" or "akinetic mutism."[2,5,10] In three of these cases the reticular substance of the midbrain was completely unaffected, while in the fourth only the dorsal portion was infarcted. In the presence of an effective functional transection of the brainstem, the integrity of the reticular substance may play a role in the apparent wakefulness in these individuals. Further studies are in progress.

In recent years, anticoagulants have been suggested with increasing frequency in the treatment of cerebrovascular disease[24,25] with particular reference to diseases of the basilar artery.[3] Such therapy was utilized in two of our cases, but in neither instance was the drug given in sufficient dose for sufficient time to produce a pharmacologic effect. In any case, there were no pathologic changes which reflected either injury or benefit from this measure. Approximately half of the infarcts in the brainstem contained sufficient hemorrhage to be grossly evident and to warrant classification as "hemorrhagic" infarcts. Parenthetically, it was noted that the spinal fluid obtained by lumbar puncture in the six cases with "hemorrhagic" infarcts of the brainstem contained no red cells in five, while the tap was con-

sidered to be traumatic in the sixth. If, as has been noted in dogs,[26] anticoagulants will increase the degree of hemorrhage within infarcts, the possibility that this therapeutic agent is harmful must be entertained. It is recognized that these infarcted zones are already necrotic and that further damage within this necrotic zone may be relatively unimportant, if one considers that anticoagulants may prevent further or new thrombosis or the propagation of a thrombus to a critical site.

SUMMARY

The clinical and pathologic features in 14 autopsied cases of occlusion of the basilar artery were studied. Most of the patients were males, past middle age. Headache, dizziness, vomiting, vertigo, visual disturbances, and dysarthria rapidly evolving to anarthria were observed and were usually followed by coma. Abnormal eye movements, fixation of the eyes in the midline with negative response to caloric stimulation, pupillary inequality, myosis, decreased or absent corneal reflexes, and facial palsy were generally present. Hemiparesis or quadriparesis, usually flaccid, at times spastic, were noted frequently, usually accompanied by hyperreflexia and a bilateral Babinski sign.

Arteriosclerosis, frequently with hemorrhage and ulceration of atheromatous plaques, and less commonly, embolism, was the etiologic factor in these occlusions. There were infarcts in the brainstem in 12 cases, in the cerebellum in four, and in the occipito-inferior temporal portions of the brain in six. The infarcts were "hemorrhagic" infarcts in approximately half of the cases, and in these cases the spinal fluid contained no blood. In two instances the basilar artery occlusion was approximately one year old. Factors related to the size and distribution of the infarcts and the long survival are discussed.

REFERENCES

1. Kingston, P. N.: Case of fatal encephalitis with hemiplegia, immediately excited by cantharides, in consequence of intense predisposition from basilar and internal carotid aneurysms. Edinburgh Med. J. 57: 69, 1842.
2. Kubik, C. S., and Adams, R. D.: Occlusion of the basilar artery—A clinical and pathological study. Brain 69:73, 1946.
3. Millikan, C. H., Siekert, R. G., and Shick, R. M.: Studies in cerebrovascular disease. III. The use of anticoagulant drugs in the treatment of insufficiency or thrombosis within the basilar arterial system. Proc. Staff Meet., Mayo Clin. 30:116, 1955.
4. Silversides, J. L.: Basilar artery stenosis and thrombosis. Proc. Roy. Soc. Med. 47:290, 1954.
5. Fang, H. C. H., and Palmer, J. J.: Vascular phenomena involving brainstem structures. A clinical and pathologic correlation study. Neurology 6:402, 1956.
6. Siekert, R. G., and Millikan, C. H.: Studies in cerebrovascular disease. II. Some clinical aspects of thrombosis of the basilar artery. Proc. Staff Meet., Mayo Clin. 30:93, 1955.
7. Paterson, J. C.: Capillary rupture with intimal hemorrhage in the causation of cerebral vascular lesions. Arch. Path. 29:345, 1940.
8. Hayem, G.: Sur la thrombose par arterite du tronc basilaire comme cause de mort subite. Arch. physiol. 1:270, 1868.
9. Denny-Brown, D., and Foley, J. M.: The syndrome of basilar aneurysm. Tr. Am. Neurol. A. 77:30, 1952.
10. Biemond, A.: Thrombosis of the basilar artery and the vascularization of the brain stem. Brain 74:300, 1951.
11. French, L. A., and Haines, G. L.: Unilateral vertebral artery ligation: Report of case ending fatally with thrombosis of the basilar artery. J. Neurosurg. 7:156, 1950.
12. Foix, Ch., and Hillemand, P.: Contribution á l'étude des ramollissement protubérantiels. Rev. méd. 43:287, 1926.
13. Lhermitte, J., and Trelles, J. O.: L'arterio sclerose du tronc basilaire et ses consequences anatomo-cliniques. Jahrb. f. Psych. Neurol. 51:91, 1934.
14. Trelles, J. O.: Les ramollissements protubérantiels. Thesis—Paris, 1934.
15. Hiller, F.: The vascular syndromes of the basilar and vertebral arteries and their branches. J. Nerv. & Ment. Dis. 116:988, 1952.
16. Marburg, O.: Ueber die neueren Fortschritte in der Topischen Diagnostik der Pons und der Medulla Oblongata. Deutsche Ztschr. Nervenh. 41:41, 1911.
17. Vander Eecker, H. B., and Adams, R. D.: Anatomy and functional significance of meningeal anastomosis of human brain. J. Neuropath. & Exper. Neurol. 12: 132, 1953.
18. Kaplan, H. A., Rabiner, A. M., and Browder, J.: Anatomical study of arteries of midbrain, pons and medulla. Tr. Am. Neurol. A. 78:56, 1953.
19. Critchley, M., and Schuster, P.: Beiträge zur Anatomie und Pathologie der Arteria cerebelli superior. Ztschr. Neurol. u. Psychiat. 144:681, 1933.
20. Atkinson, W. J.: The anterior inferior cerebellar artery. Its variations, pontine distribution and significance in the surgery of cerebello-pontine angle tumors. J. Neurol., Neurosurg. & Psychiat. 12:137, 1949.
21. Denny-Brown, D.: The treatment of recurrent cerebrovascular symptoms and the question of "vasospasm." M. Clin. North America 35:1457, 1951.
22. Denny-Brown, D.: Basilar artery syndromes. Bull. New England M. Center 15:33, 1953.
23. Denny-Brown, D.: Recurrent cerebrovascular symptoms of vasospasm. Arch. Neurol. & Psychiat. 67: 117, 1952.
24. Wright, I. S., and McDevitt, E.: Cerebral vascular diseases: Their significance, diagnosis and present treatment, including the selective use of anticoagulant substances. Ann. Int. Med. 41:682, 1954.
25. Foley, W. T., McDevitt, E., Symon, C., and Wright, I. S.: Further experience with long term anticoagulant therapy. Arch. Int. Med. 95:487, 1955.
26. Moyes, P. D., Millikan, C. H., Wakins, K. S., Sayre, G. P., and Whisnant, J. P.: Influence of anticoagulants on experimental canine cerebral infarcts. Proc. Staff Meet., Mayo Clin. 32:124, 1957.

CASE REPORT

Intrathoracic Meningocele

Paul Teng, M.D. and Peter Eastman, M.D.

MENINGOCELE commonly occurs in the posterior midline along the craniospinal axis. Rarely, it may occur on the ventral surface of the spinal column through a defect in the sacral spine or in the extrapleural space lateral to the spinal column. Twenty-three cases have been described in the latter location. The rarity of the lesion justifies this report of a twenty-fourth case, and we have included a brief review of the literature to date.

CASE REPORT

A 34 year old man was admitted to the hospital on May 17, 1956 because of a mass shadow found in the right upper chest in a routine chest film. In spite of its size, he was asymptomatic.

Physical examination on admission revealed a mild degree of scoliosis of the thoracic spine. Percussion showed an area of dullness in the right paravertebral region above the third intercostal space. All other findings of the neurologic and bronchoscopic examination were essentially negative.

Roentgenogram of the chest showed a sharply demarcated spherical shadow above the second rib in the right upper chest (figure 1). It measured two and a half inches in diameter and was located in the posterior mediastinum, extending to the left pleural cavity. The trachea was seen in its normal position. The ribs adjacent to the intra thoracic mass showed no erosion. The spine showed an absence of pedicles on the right side from C_7 to D_3, and the D_4 pedicle was markedly narrowed. The intervertebral foramen of D_1 to D_3 formed one large elongated defect. The right side of the D_3 vertebral body was scalloped.

Other laboratory findings, including examination of urine and blood, were noncontributory. Because of the lack of neurologic signs indicating spinal cord involvement, a lumbar puncture was not done.

The preoperative diagnosis was mediastinal tumor, possibly a neurofibroma.

On May 23, 1956 a right thoracotomy was performed through a posterolateral incision, with the resection of the third rib. A bilobulated cystic mass was exposed in the posterior mediastinal gutter. It extended into the chest cavity behind the pleura. The mass measured 2 by 2 by 3 inches and was bisected by the portion of the third rib posterior to its neck. It pulsated with respiration and was pale in color. Aspiration of the cyst revealed clear fluid. The overlying parietal pleura was reflected and the cyst incised. When opened, a segment of the spinal cord about two and a half inches long was visualized through the elongated defect formed by the confluence of the D_1 to D_3 intervertebral foramina. The spinal cord looked normal. It was confined in the spinal canal without distortion or herniation. The dentate ligament on the exposed side of the spinal cord was missing. The spinal dura was in continuity with the meningocele. The meningocele opened into the spinal subarachnoid space through the defect of the spinal canal and the dura which formed its neck. A purse-string suture was applied to the neck of the sac and the wall of the meningocele was partially excised. The stump was inverted into the spinal defect. The pleura flaps were resutured. The chest wall was closed in layers with cotton sutures. A No. 24 plastic catheter was inserted through the eighth interspace in the anterior axillary line and led to an underwater drainage.

FIG. 1. Chest roentgenogram shows a round shadow (meningocele) in the right superior paravertebral region.

From the neurosurgical service and the department of surgery, Kaiser Foundation Hospital, Los Angeles, California.

TABLE I—ANALYSIS OF REPORTED CASES

Case No.	*Author & Year*	*Sex*	*Age*	*Evidence of Neuro-Fibromatosis*	*Site of Meningocele*	*Clinical Symptoms*	*X-ray Change of Spine or Rib*	*Diagnostic Procedure Used*	*Preoperative Diagnosis*	*Treatment & Result*
1	Pohl, 1933[1]	F	47	Yes	D_4, Rt.	None	Erosion of rib and vertebral body		Intrathoracic Neurofibroma	Died postoperatively, Empyema and meningitis
2	Schueller & Uiberall, 1938[2]	M	56	Yes	D_5, Rt.	Chest pain, paraplegia	Ditto enlarged foramina	Myelogram	Meningocele	Neurectomy for pain. Died after operation
3	Ameuille et al., 1940[3]	F	46	No	D_8-D_9, Rt.	None	Ditto		Hydated cyst	Surgical removal; died, empyema and meningitis
4	Campos, 1946	M	7		D_6, Rt.		Bifid, Dorsal spine synostosis and other anomalies			
5		M	54	Yes	D_8	Chest pain, cough, dyspnea	Enlarged foramina D_{8-5}		Neurofibroma	
6	Welch et al., 1948[5]	F	41	Yes	D_6 Lt.	None	Ditto, erosion of spine & rib		Neurofibroma	Surgical removal
7	Seugpiel et al., 1948[6]	M	21	No	D_1, D_2, Rt.	None	Ditto		Neurofibroma	Thoracotomy; meningocele not removed
8	Byron et al., 1949[7]	F	36	Yes	D_2, D_3, Rt.	Cough, dyspnea, Chest pain	Ditto		Neurofibroma	Surgical removal
9		M	21		Rt. apex	None			Neurofibroma	Thoracotomy, not removed. Surgical removal
10		M	61	Yes	Rt. apex	Neck pain	Ditto		Neurofibroma	Died
11	Mendelsohn 1949[8]	F		Yes		None			Neurofibroma	Operation, no detail
12	Head 1949[9]	M	43		Lower dorsal left	None		Direct puncture	Meningocele	No operation
13	Ciaglia 1949[10]	F	31	Yes	Lt. apex	None	Ditto			Ligation of pedicle of meningocele
14	Cross et al., 1949[11]	M	23	Yes	D_8-D_{10}	Back pain	Anterior displacement, D_{10}	Myelogram	Meningocele	No operation
15	Lippman-Kessl 1951[12]	F	23	No	D_5-D_7, Lt.	Chest pain; sensory change	Scalloping & wedging vertebral body; rib erosion		Neurofibroma	Surgical removal
16		F	8½	Yes	D_7-D_8	Paraplegia	Ditto		Neurofibroma	Exploration; meningocele not removed
17	Ottani, 1951[13]				Upper posterior mediastinum			Direct puncture	Meningocele	No operation
18	Schlumberger 1951[14]	M	63		"Border of heart"	Cough	Widening foramina. Erosion of vertebral body			Operation; no detail
19	Rubin & Stratemeir 1952[15]		7 wks.		D_4-D_5, Rt.	Dysphagia	Bifid vertebral bodies; synostosis D_5-D_6			Autopsy material
20	Hackenseliner & Pape, 1954[16]			Yes	Lower dorsal, left	Pain, paralysis	Posterior scalloping of body; erosion or rib; enlarged foramina	Direct puncture; Myelogram	Meningocele	
21				Yes	Lower thoracic	Pain	Ditto	Direct puncture	Meningocele	
22	Gernez-Rieux & Lepaul, 1955[17]	M	59	Yes	D_9, Rt.	Chest pain		Direct puncture	Meningocele	
23	Laitinen & Turunen, 1955[18]			Yes	D_8-D_9, Lt.		Ditto	Air myelogram	Meningocele	Surgical removal
24	Author's Case 1957	M	48	Yes	D_2-D_3, Rt.	None	Ditto		Neurofibroma	Surgical removal

A careful search of the body surface revealed no cafe-au-lait spots or subcutaneous nodules suggestive of von Recklinghausen's disease. Nevertheless, the biopsy of a small tumor found in the posterior right occipital region revealed a neurofibroma. The postoperative course was uneventful, and the patient was discharged from the hospital on June 2, 1956. A chest film one year after operation showed no evidence of recurrence.

ANALYSIS OF REPORTED CASES

Twenty-four cases of intrathoracic meningocele, including one presented here, have been reported in the literature since 1933.[1–18] Among these 24 patients were 11 males and eight females, with five not specified. The age varied from seven weeks to 63 years.

Clinical evidence of von Recklinghausen's disease was mentioned in 15 cases. Five patients showed no evidence of neurofibromatosis, and there were four cases with no detail.

The meningocele was found in the upper thoracic cavity above the level of D_6 in 14 cases, and in the lower portion of the chest in ten cases. In 11 cases it was found in the right pleural cavity, in seven cases in the left, and not specified in six cases.

Nine patients were asymptomatic. The intrathoracic meningocele was an accidental finding in a routine physical examination or chest film. Twelve patients presented symptoms, such as pain varying from dull ache to sharp pain of radicular type, dyspnea, dysphagia, irritative cough, paraplegia, and/or impairment of sensations below the level of the lesion. There was no detail in the other three cases.

Bone changes seen on roentgenography have been described in 19 of these 24 patients. The characteristic changes in the majority of these cases were erosion of the neighboring ribs, erosion or scalloping of the posterior portion of the vertebral body, erosion or enlargement of intervertebral foramina, erosion or absence of pedicles, and scoliosis of the dorsal spine. In two cases bifid vertebrae and synostosis were noted.

There was no specific change noted in the study of the cerebrospinal fluid. The cellular and protein contents were normal. A manometric block was demonstrated in two cases.

Specific diagnostic procedures were used in eight of these cases, consisting of a myelogram in four cases, including one air myelogram and five direct puncture aspirations of the cyst.

The preoperative diagnosis was neurofibroma in 11 cases, hydatid cyst in one, and intrathoracic meningocele in nine; in three cases the diagnosis was not mentioned. An accurate diagnosis of intrathoracic meningocele was made in two out of 14 instances before the year 1950. From 1951 to 1957 six out of ten cases were diagnosed correctly with the aid of a properly selected diagnostic procedure.

Thirteen cases were operated on, with removal of the meningocele in ten cases. Two died from postoperative infection. Both of these occurred prior to the era of antibiotic therapy. Following removal of the meningocele, no recurrence has been reported.

DISCUSSION

The frequent association of neurofibromatosis and intrathoracic meningocele has led to a hypothesis that the formation of the meningocele is secondary to an intrathoracic neurofibroma. The deformity of the vertebrae is attributed to aneurysmal action of a periosteal neurofibroma. The defect in the wall of the spinal canal, therefore, leads to the formation of an intrathoracic meningocele.[19] This is highly hypothetical. First, neurofibromatosis is a common disease. It occurs in about one in 200 of the general population. Approximately one in every ten cases shows skeletal changes and in half of these patients the spine is involved.[20] Yet, intrathoracic meningocele remains a rare disease. Second, a defect in the vertebrae alone does not lead to the formation of a meningocele. As in the case of lumbosacral meningocele, a spina bifida is always an associated bone defect, yet spina bifida often exists without evidence of a meningocele and it does not lead to the formation of a meningocele later in life. Furthermore, a surgical defect of the spinal canal produced in neurosurgical procedures does not cause the formation of a meningocele. Third, respiratory action or intrathoracic pressure can hardly be an attributory factor in the formation of an intrathoracic meningocele in the presence of a defect in the lateral wall of the spinal canal. If this were true, a lateral intrathoracic meningocele might be expected to recur soon after its excision and repair. The recurrence of an intrathoracic meningocele after surgery has not yet been reported. Fourth, in none of the reported cases of intrathoracic meningocele has any evidence of a neurofibroma been described in the vicinity of the bone defect or the meningocele. Fifth, many patients had an intrathoracic meningocele but showed no evidence of von Recklinghausen's disease.

Lipmann-Kessel advanced the theory that in von Recklinghausen's disease the spinal de-

formity may be due to the prolonged aneurysmal action of an undisclosed meningocele or of an intrathoracic dilation of the dura mater.[11]

Cross[12] suggested that the intrathoracic meningocele originates from a diseased or defective dura and the bone change is secondary. Ameuille's[3] case supported the latter view. The gross dilation and sacculation of the spinal dura were well demonstrated.

As shown in table 1, an intrathoracic meningocele was found in all age groups. Bone defects were seen in young patients as well as in the old. A lateral intrathoracic meningocele is analogous to the meningocele found elsewhere in the body. It is probably a result of a developmental defect in the dura and the bony enclosure, only it is in a hidden location. It does not involve the nerve roots and is well protected from a spontaneous rupture. It may remain asymptomatic for many years until discovered in a routine physical check-up. It may cause symptoms by pressure upon the neighboring organs, spinal cord, intercostal nerves, trachea, esophagus, or heart and its large vessels. The bone defect enlarges as the cyst grows. Its growth is slow. Its frequent association with von Recklinghausen's disease remains unexplained, though it can hardly be dismissed as a coincidence.

Although cases of intrathoracic meningocele have been reported infrequently, it has attracted the attention of clinicians. This is indicated by the increasing incidence of a correct preoperative diagnosis made after the year 1951, in comparison with the earlier period. The bone changes observed on roentgenograms are by no means characteristic of an intrathoracic meningocele. An aneurysm or a neurofibroma may cause similar changes in the vertebrae. These two conditions can be differentiated easily by a direct puncture aspiration or a myelographic study.

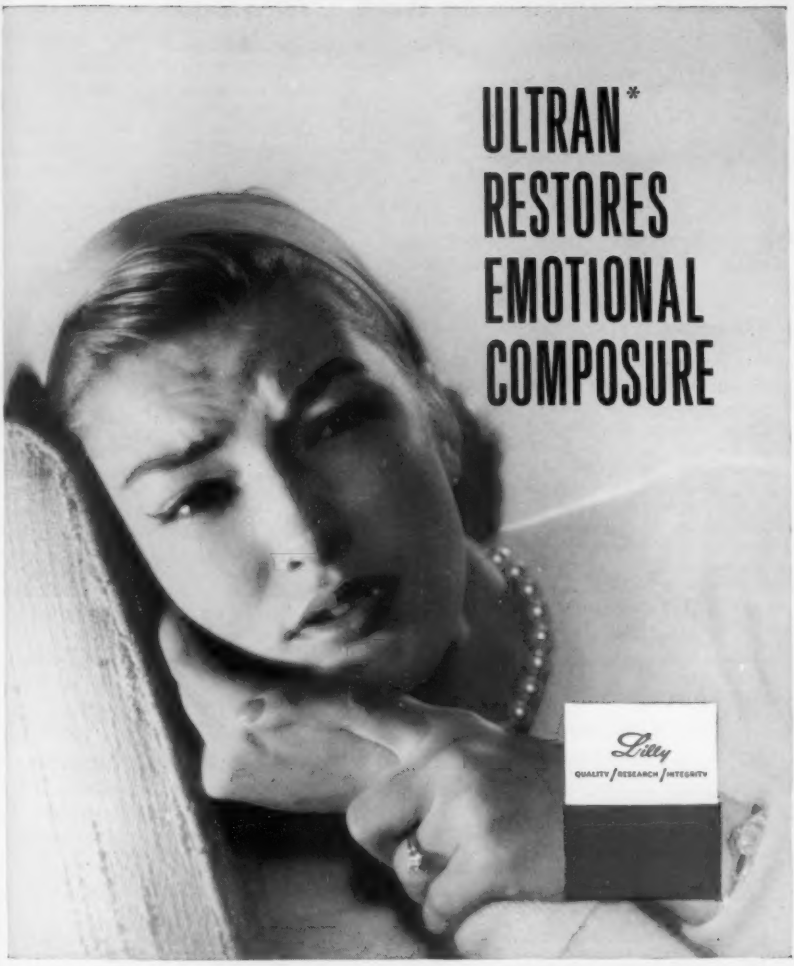
It is not necessary to remove an asymptomatic intrathoracic meningocele, but those which cause pressure symptoms should be removed and repaired surgically. In case the intrathoracic meningocele was an accidental finding during exploratory thoracotomy as a result of preoperative misdiagnosis, as in our patient, it should be removed and repaired in spite of its asymptomatic nature. This will prevent a second major operation, should the meningocele cause symptoms in the future.

SUMMARY

A case of lateral intrathoracic meningocele is described, with a brief review of the literature.

REFERENCES

1. Pohl, R.: Meningocele im Brustraum unter dem Bilde eines intrathorakalen Rundschattens. Roentgenpraxis 5:747, 1933.
2. Schueller, A., and Uiberall, H.: A case of neurofibromatosis–Recklinghausen combined with lateral spinal meningocele. Confinia neurol. 1:312, 1938.
3. Ameuille, P., Wilmoth, P., and Kudelski, C.: Méningocèle rachidienne à dévelopement intrapleural. Bull. et mém. Soc. méd. hôp. Paris 56:608, 1940
4. Campos, J. M. C.: Meningocele intratorácico. Bol. San Sao Lucas 8:40, 1946.
5. Welch, S., Ettinger, A., and Hecht, P. L.: Recklinghausen's neurofibromatosis associated with intrathoracic meningocele. New England J. Med. 238: 622, 1948.
6. Seugpiel, G. W., Ruzicka, F. F., and Lodwell, E. A.: Lateral intrathoracic meningocele. Radiology 50: 515, 1948.
7. Byron, F. X., Alling, E. E., and Samson, P. C.: Intrathoracic meningocele. J. Thoracic Surg. 18:294, 1949.
8. Mendelsohn, H. J., and Kay, E. B.: Intrathoracic meningocele. J. Thoracic Surg. 18:124, 1949.
9. Quoted in the article of Byron.[7]
10. Quoted in the article of Byron.[7]
11. Lipmann-Kessl, A. W.: Intrathoracic meningocele, spinal deformity and multiple neurofibromatosis. J. Bone & Joint Surg. 33-B: 87, 1951.
12. Cross, G. O., Reavis, J. R., and Saunders, W. W.: Lateral intrathoracic meningocele. J. Neurosurg. 6: 423, 1949.
13. Ottani, G.: Meningocele intratoracico. Ann. radiol. diag. 23:416, 1951.
14. Schlumberger, H. G.: Tumors of the mediastinum. Armed Forces Institute of Pathology F 18:86, 1951.
15. Rubin, S., and Stratemeir, E. H.: Intrathoracic meningocele. Radiology 58:552, 1952.
16. Hackensellner, H. A., and Pape, R.: Meningocele bei Neurofibromatosis Recklinghausen. Fortschr. Geb. Roentgenstrahlen 81:66, 1954.
17. Gernez-Rieux, Ch., and Lepaul, G.: Les méningocèles à dévelopement intrathoracique. J. franc. méd. et chir. thorac. 8:633, 1954.
18. Laitinen, H., and Turunen, M.: Diagnosis of intrathoracic meningocele. Dis. Chest. 27:547, 1955.
19. Brooks, B., and Lehman, E. P.: Bone changes in Recklinghausen's neurofibromatosis. Surg., Gynec., & Obst. 38:587, 1924.
20. Preiser, S. A., and Davenport, C. B.: Multiple neurofibromatosis (von Recklinghausen's disease) and its inheritance: with description of a case. Am. J. M. Sc. 156:507, 1918.



anxiety and tenseness quickly allayed

'Ultran' is beneficial in a wide range of conditions. It may reduce the severity of or eliminate anxiety-tension states and the anxiety associated with such conditions as primarily organic diseases, emotional instability, menopause syndrome, premenstrual tension, and insomnia.

'Ultran' is well tolerated and relatively safe. It is also chemically different from all other tranquilizers.

Pulvules of 300 mg.; usually 1 t.i.d.

*"Ultran" (Phenaglycodol, Lilly)

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.

874018

Products and Services

The information below was supplied by the manufacturers

DISPOSABLE TRANSFUSION SET

A safer and easier to use administration set for transfusions of blood, plasma, or serum has been introduced by Abbott Laboratories, North Chicago, Illinois. The new disposable set has a bulb-shaped pump which permits the administrator to control instantly the rate of fluid flow to the patient.

To administer a steady stream of fluid, the operator squeezes the bulb. The rate of flow depends upon the pressure exerted on the bulb. When the bulb is released, the fluid returns to drip administration at a predetermined rate. The drip chamber does not flood, so the administrator can easily observe the rate of drip or flow.

Because pressure ends when the bulb is released, the new pump is safer than systems using compressed air. Other safety features include a check valve between the pump outlet and the patient to prevent withdrawal of blood from the patient, and placement of the filter in the drip chamber instead of in the pump so that pressure is not applied to unfiltered blood. About 25 squeezes of the pump, which has a capacity of 30 cc., will empty a 600 cc. container of fluid.

FLEXIN COMBINED WITH ANALGESIC

Flexilon, a new combination skeletal muscle relaxant and analgesic, has been introduced by McNeil Laboratories, Inc., Philadelphia. The new product combines Flexin zoxazolamine, and Tylenol acetaminophen. Relief of muscle spasm is accomplished by Flexin, while Tylenol provides the analgesic effect. Each Flexilon tablet contains 125 mg. of Flexin and 300 mg. of Tylenol. Flexilon tablets are enteric coated, which delays the pharamacologic effects four to five hours and minimizes the likelihood of gastric upsets.

Flexin, an orally effective skeletal muscle relaxant, is believed to act by selective inhibition of polysynaptic pathways in the central nervous system. This "lissive" action, which does not interfere with normal muscle power, appears to take place in the spinal cord and subcortical centers. By relieving pain, Tylenol augments the lissive action of Flexin. Flexilon is indicated for the treatment of orthopedic and rheumatic disorders such as: muscle strains and sprains, low back pain, osteoarthritis, fibrositis, myositis, bursitis, spondylitis, rheumatism and myalgias, rheumatoid arthritis, neuritis, tenosynovitis, torticollis, and menopausal arthralgia.

(Continued on page 22A)

ULTRASOUND . . . . .

ULTRASOUND . . . . .

ULTRASOUND IN BIOLOGY AND MEDICINE

A distinctive contribution to a new field of basic and clinical research, *Ultrasound in Biology and Medicine* is Volume III in the new Symposium Proceedings Series of the American Institute of Biological Sciences.

The Symposium was held June 1955 at Allerton Park, Monticello, Illinois, under the auspices of the Bioacoustics Laboratory of the University of Illinois and the Physiology Branch of the Office of Naval Research. The papers presented and the discussions that followed have been edited by Elizabeth Kelly.

Acoustic Properties of Blood and its Components, E. L. Carstensen and H. P. Schwan; Physical Aspects of High Amplitude Sound Phenomena, W. L. Nyborg; Progress in the Techniques of Soft Tissue Examination by 15MC Pulsed Ultrasound, J. J. Wild and J. M. Reid; Techniques Used in Ultrasonic Visualization of Soft Tissues, D. H. Howry; The Indications and Contra-indications for Ultrasonic Therapy in Medicine, J. H. Aldes; Neurosonic-surgery, W. J. Fry and F. J. Fry; Histological Study of Changes Produced by Ultrasound in the Gray and White Matter of the Central Nervous System, J. W. Barnard, J. F. Brennan and W. J. Fry; On the Problem of Dosage in Ultrasonic Lesion Making, H. T. Ballantine, Jr., W. C. Cotter and T. F. Hueter; Some Examples of Ultrasonic Frequency Sensitive and Frequency Insensitive Biological Reactions, Rene-Guy Busnel; A Forum on an Ultrasonic Method for Measuring the Velocity of Blood, E. J. Baldes, W. R. Farrall, M. C. Haugen and J. F. Herrick; Destructive Effects of High-intensity Ultrasound on Plant Tissues, J. F. Lehmann, E. J. Baldes and F. H. Krusen; Generating and Measuring High-intensity Ultrasound of Frequencies Between 1 and 68 Megacycles, B. B. Chick; Some Changes in Liver Tissue which Survives Irradiation with Ultrasound, E. Bell; An Ultrasonic Dosage Study; Functional Endpoint, F. Dunn and W. J. Fry; Thermocouple Probes, W. J. Fry.

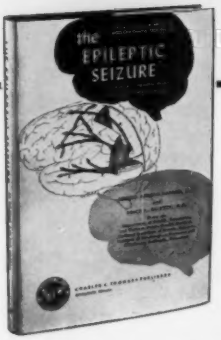
$4.75 **$3.75 (AIBS Members)**

Orders should be placed with:

AMERICAN INSTITUTE OF BIOLOGICAL SCIENCES

2000 P Street, N.W. **Washington 6, D.C.**

A clinical-electrographic analysis of Metrazol-induced attacks



THE EPILEPTIC SEIZURE

Its Functional Morphology and Diagnostic Significance

In this book NEUROLOGISTS, NEUROSURGEONS, ELECTROENCEPHALOGRAPHERS, and all INVESTIGATORS who have a particular interest in the field of the epilepsies and of brain physiology will find a SOLUTION to their PROBLEMS.

- **The pattern of the entire epileptic seizure** is studied in detail, and emphasis is placed not only upon the different signs but also upon their temporal relationship in the course of the attack.
- **Pre-ictal, ictal and post-ictal clinical symptoms** are discussed and integrated with their electrographic correlates.
- Various **"seizure formulae"** are eventually composed on the basis of these clinical-EEG criteria, obtained in a series of patients in which the correct diagnosis had been previously established in all cases and subsequently confirmed at operation in the large majority.

A critical and detailed review of *purposes, method and results of the EEG activation with Metrazol administration* is provided. The usefulness of inducing, observing and recording a clinical seizure in all the cases of epilepsy which are possible candidates for surgical treatment, is emphasized with convincing evidence.

Evidence offered to show the almost constant identity between the seizure patterns characterizing the spontaneous fit in a given patient and the Metrazol-induced attack in the same subject.

COSIMO AJMONE-MARSAN, M.D.
and
BRUCE L. RALSTON, M.D.
From the Department of Health, Education and Welfare,
Public Health Service
National Institutes of Health
National Institute of Neurological Diseases and Blindness
Bethesda, Maryland

264 pages (6 x 9), 60 illustrations
Sent on approval, $6.00
Published in 1957

CHARLES C THOMAS • PUBLISHER
301-327 East Lawrence Avenue
Springfield, Illinois

"The devil

still talks to me

but I don't bother to holler back. . . ."[1]

Manic, hallucinating . . . In acute psychotic agitation, the direct purpose of SPARINE is to quiet the hyperactivity. When hallucinations are present, they are either abolished or made less important and less frightening to the patient.

SPARINE is a well-tolerated and dependable agent when used according to directions. It may be administered intravenously, intramuscularly, or orally. Parenteral use offers (1) minimal injection pain; (2) no tissue necrosis at the injection site; (3) potency of 50 mg. per cc.; (4) no need for reconstitution before injection.
Comprehensive literature is available on request.

1. Fazekas, J.F., et al.: J.A.M.A. *161*:46 (May 5) 1956.

Wyeth®
Philadelphia 1, Pa.

Sparine®

HYDROCHLORIDE

Promazine Hydrochloride — *10-(γ-dimethylamino-n-propyl)-phenothiazine hydrochloride*

PRODUCTS AND SERVICES

(Continued from page 18A)

EFFECTS OF TRANQUILIZING DRUGS ON NORMAL PERSONS

The widespread use of tranquilizers outside hospitals is noted as justification for extensive research to determine their effects on the physical, intellectual, and sensorimotor abilities of persons who continue their normal daily activities after taking the drugs, according to a recent report by Donald G. Marquis of the Mental Health Research Institute at University of Michigan.

Tests conducted by the National Institute of Mental Health with chlorpromazine indicate that the drug may produce impairment of performance of normal persons in a series of tasks requiring sustained attention and perceptual discrimination.

In tests with meprobamate (Miltown) conducted at the Mental Health Research Institute to determine possible effects of the drug on skills required for safe driving, twice the usual single dose was found to produce no detrimental effect on the sensorimotor and attention skills. When given with alcohol, the drug did not increase the unfavorable effect produced by the alcohol. Additional studies conducted in Sweden are cited which corroborate these findings.

It is also suggested that tranquilizing drugs may vary in effect from one person to another. Tests conducted at Massachusetts General Hospital are reviewed which show that this appears to be true of sedatives, such as morphine and pentobarbital, and amphetamine. According to Rorschach data, those persons who responded in an atypical manner—for example, with euphoria to pentobarbital and sedation to amphetamine—tended to be immature, impulsive, lacking in control, high in anxiety and hostility, and unrealistic in striving for achievement beyond their capabilities.

Personality tests given the subjects in the National Institute of Mental Health chlorpromazine studies indicated that those whose performance was most affected by the drug were in general those who scored highest on the psychopathic deviate scale, while those who reported the greatest subjective effects were highest on the depression scale (MMPI). It was further shown that no significant correlation could be found between objectively measured effects and the subjective effects reported by questionnaire, indicating that the subjects were unable to gauge the degree of possible impairment of mental function resulting from administration of chlorpromazine.

(Continued on page 26A)

JOSIAH MACY, JR. FOUNDATION

Announces two new books

GROUP PROCESSES

Transactions of the Third Conference

Edited by Bertram Schaffner,
University Seminar on Communications, Columbia University

The discussions in this volume are concerned with interpersonal influences within the family, interpersonal persuasion, further studies on maternal-neonate relationships, and Chinese Communist thought reform. **$4.00**

NEUROPHARMACOLOGY

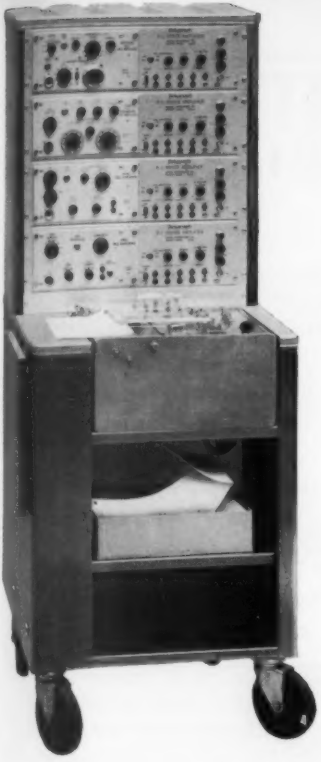
Transactions of the Third Conference

Edited by Harold A. Abramson, The Long Island Biological Association,
Cold Spring Harbor and The State Hospital, Central Islip, N. Y.

The discussions in this conference dealt with blocking of the LSD-25 reactions in Siamese fighting fish, LSD-25 reaction in snails, stress situations in animals and conflict situations in humans, measurements of subjective responses, studies of effects of psychosomimetic drugs in animals and man, LSD-25 and its selective affinity for depressing dendritic activity, serotonin and norepinephrine as antagonistic chemical mediators regulating the central autonomic nervous system, effects of chlorpromazine and reserpine on the rat, the production and control of alcohol cravings in rats, and the action of alcohol on the central nervous system. **$4.50**

JOSIAH MACY, JR. FOUNDATION PUBLICATIONS
16 WEST 46th STREET, NEW YORK 36, NEW YORK

Please make checks payable to Josiah Macy, Jr. Foundation



NEW

GRASS
MODEL 5
POLYGRAPH
FOR
VERSATILE
RECORDING
IN
PHYSIOLOGY
PHARMACOLOGY
ANESTHESIOLOGY
PSYCHOLOGY

- The Polygraph records blood pressure, oxygen tension, CO_2, plethysmogram, respiration, temperature PGR, EMG with integration, EKG and/or heart rate, EEG and other physiological data.
- Interchangeable Preamplifiers, designed specifically for each application, plug into identical Driver Amplifiers.
- Amplitude of direct-writing oscillographs is 50 mm with 2% linearity.
- Two channel teaching and six channel research models available.
- Built to Grass precision standards to insure dependability and accuracy for years of service.

GRASS INSTRUMENT COMPANY

101 OLD COLONY AVENUE - QUINCY, MASS.

INSTRUMENT MAKERS TO THE MEDICAL PROFESSION SINCE 1935

Founded 1879

RING SANATORIUM

Eight miles from Boston

For the study, care and treatment of emotional, mental, personality and habit disorders.

On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring medical, psychiatric, or neurological supervision.

Full resident and associate staff. *Courtesy privileges to qualified physicians.*

BENJAMIN SIMON, M.D.
Director

CHARLES E. WHITE, M.D.
Assistant Director

Arlington Heights, Massachusetts **Telephone MIssion 8-0081**

Accredited by the APA and the Joint Commission on Accreditation of Hospitals

complete integrated facilities for

ELECTROMYOGRAPHY

- **SINGLE CHANNEL EMG** with two-channel magnetic tape recorder for recording notes and EMG simultaneously. Model TE 1.2-7
- **TWO-CHANNEL EMG** permits simultaneous recording and study of two EMG potentials or of one potential together with a related physical parameter such as force or pressure. Model TE 2-7

● Automatic controls and new circuits provide simplified reliable operation without shielded rooms in most locations. ● EMG potentials faithfully reproduced by special recorder circuits. ● Specifications equal or surpass requirements for research, teaching and clinical use.

NEW rugged COAXIAL NEEDLE ELECTRODE withstands autoclaving, has tapered shaft, 26 gauge at tip, insulated handle.

TECA CORPORATION

80 Main St.
White Plains
New York

NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

Francis M. Forster, President
Augustus S. Rose, President-Elect
A. L. Sahs, Vice-President
Joseph M. Foley, Secretary
Charles Van Buskirk, Treasurer

FEBRUARY 1958

Preview of AAN Scientific Sessions The skeleton structure of the scientific program for the 1958 annual meeting of the Academy is unfolding. The scientific presentations of this meeting, to be held in Philadelphia's Bellevue-Stratford Hotel (April 24-26), will comprise four parts: general neurologic papers; section presentations in neurochemistry, neuropharmacology, and neuroanatomic sciences; a research symposium; and reports by speakers from here and abroad. About 60 papers will be presented in the general sessions beginning Thursday morning (April 24), continuing all day Friday (April 25), and ending Saturday afternoon (April 26).... The neurochemistry section (Donald B. Tower, section chairman, and Roscoe O. Brady, program chairman) will have two symposia, one Thursday afternoon (April 24) on the neurochemistry of the nucleotides, with Morris Friedkin serving as moderator, and the other on neurochemistry of amino acids on Friday morning (April 25), Eugene Roberts, moderator. The topic of the neuropharmacology section (James Toman, section chairman), to be held Thursday afternoon (April 24), is "Pharmacologic Stimulation of the Central Nervous System." The section on neuroanatomic sciences, under the chairmanship of Ray Snider, will hold a symposium on the cerebellum (April 24).... The fourth annual symposium of inquiry sponsored by the research committee, developed by Chairman Ward Halstead, will be held Thursday night (April 24). This symposium will center on higher brain functions, with presentations on the neuromechanisms of memory (Roland Myers); sensory deprivation (Austin Riesen); and the neuromechanisms of disturbances in thinking (Ralph Reitan).... Among the special speakers will be Sir Russell Brain and Dr. J. G. Greenfield, both of London; Bernard J. Alpers, Paul I. Yakovlev, Malcolm B. Carpenter, and Lawrence Kubie. The titles of their presentations have not as yet been announced, except for Dr. Kubie who will speak on "A New Model for Human Psychological Processes," in which he will bring up to date his original concept on reverberating circuits which originally appeared in BRAIN in 1915.... The chairman of the 1958 AAN scientific program is Dr. Gilbert H. Glaser, Professor of Neurology, Yale University School of Medicine, New Haven 11, Conn.

New Board Diplomates At the New York examinations (Dec. 16-17, 1957) of the American Board of Psychiatry and Neurology, 19 candidates were certified in neurology: Kittridge Anderson, Montgomery; Stanley Martin Ball, Albany; David I. Biser, New York

(supplementary certification); James William Crawley, Houston; Anatole S. Dekaban, Bethesda; Gregory Stark Ferriss, New Orleans; Murray Glusman, New York (supplementary certification); Edward Jimenez-Pabon, San Juan, Puerto Rico; Henry Leffman, Mercer Island, Wash.; Lowell Gerald Lubic, Pittsburgh; David Frey Mendelson, Minneapolis; De Saussure Ford Philpot, Jr., New York (supplementary certification); Charles M. Poser, Kansas City; Ernst A. Rodin, Ann Arbor; Lawrence Stark, New Haven; Joseph M. Stein, Topeka; John O. Strom, Providence; H. Richard Tyler, Boston; Jack Page Whisnant, Rochester.... Among the new officers of the board elected at this meeting were: Russell N. DeJong, president, and Paul I. Yakovlev, vice-president. David A. Boyd, Jr., continues as secretary-treasurer. Hugh Carmichael was elected to fill the expired term of George N. Raines as one of the directors of the board (representing the AMA).

Netsky Becomes Neurology Professor at Bowman Gray Martin G. Netsky has been appointed professor of neurology in the Bowman Gray School of Medicine of Wake Forest College and director of the section on neurology, succeeding Richard L. Masland, who is now assistant director of the National Institute of Neurological Diseases and Blindness. Netsky, a graduate in medicine of the University of Pennsylvania, has been a member of the Bowman Gray Faculty since 1955, when he was appointed associate professor of neurology and professor of neuropathology. Previously, he was on the neurologic staff of the Montefiore Hospital in New York (1946-1955) and associate in neurology at Columbia University College of Physicians and Surgeons (1949-1955). ...In collaboration with Dr. Weston Kelsey, professor of pediatrics, Dr. Netsky is initiating a special training program in pediatric neurology. He will continue his research program in experimental neuropathology, which includes studies of heavy metal intoxication, as well as investigations of the dynamics of the cerebral circulation, especially in relation to experimental cerebral vascular occlusions.

Visit to the Neurologic Institute in Milan In Milan, the teeming industrial center of Italy, there is a neurologic institute which ranks high among the leading neurologic hospitals of Europe. It is called "Istituto Neurologico C. Besta," named after its founder and inspirator, Professor Carlo Besta. Founded in 1922 and given the status of "Ente Morale" (public institution) in 1923, it was honored in 1952 by being nominated "Istituto a carattere scientifico" (scientific institution) by the Italian Minister of Health. An autonomous unit, the institute claims to be the only hospital in Italy devoted exclusively to the study and treatment of neurologic disorders.... Your reporter, in the company of Cosimo Ajmone Marsan of the National Institute of Neurological Diseases and Blindness, Bethesda, had the privilege

to visit this interesting hospital, escorted by two former pupils of Professor Besta, Professor Giuseppe Vercelli and Professor Rinaldo Grisoni, who are now, respectively, director and vice-director of the institute. Also, joining us on the tour was Professor Giulio Morello, the chief neurosurgeon, and Professor Fermo Mascherpa, who with Guido Lombardi, directs the department of neuroradiology. Finally, we were introduced to Professor Colli-Grisoni, who directs the institute's cerebral palsy rehabilitation center.... During the visit at the institute, it did not take long to sense its intensely busy and well integrated activities in clinical neurology and research. Interdisciplinary coordination was exceptionally high; there was close collaboration of neurology with neurosurgery, and of both with neuroradiology, electroencephalography and neurophysiology, and the rehabilitation institute. The physical facilities and equipment were of highest standard. The pace of their activity is well reflected in the hospital figures of 1954 to 1955: 4,897 inpatients, 9,887 outpatients, 731 arteriograms, 1,189 pneumoencephalograms, 87 ventriculograms, 164 myelograms, 5,564 electroencephalograms, and 501 neurosurgical operations. The continued growth of the Istituto Neurologico C. Besta was evident by construction then under way for a new wing to house additional patient quarters and laboratories.

ARNMD Elects New Officers Following its scientific sessions on "The Effect of Pharmacologic Agents on the Nervous System," the Association for Research in Nervous and Mental Disease at its thirty-seventh annual meeting (Hotel Roosevelt, New York, Dec. 13-14) elected L. M. Eaton, president; Raymond D. Adams, and G. Milton Shy, vice-presidents; Rollo J. Masselink and Lawrence C. Kolb continue as secretary-treasurer and assistant secretary, respectively.... The ARNMD topic for 1958 is disorders of muscle.

MS Society Re-elects Chairman At their 23rd semiannual meeting in the Hotel Biltmore, New York, the Medical Board of the National Multiple Sclerosis Society re-elected Augustus S. Rose as chairman and H. Houston Merritt as vice-chairman. Following its rotation policy, the society has forwarded invitations to become new members of the board to: Thomas L. Auth, G. Milton Shy, Fred Plum, Gordon H. Scott, Peritz Scheinberg, A. M. Rabiner, Frederick L. Stone, Gilbert H. Glaser, and Morton D. Marks.

Myasthenia Advisory Board Holds Scientific Session Preceding the business sessions of its annual meeting in the Hotel Roosevelt, New York (Dec. 13), the Medical Advisory Board of the Myasthenia Gravis Foundation conducted scientific sessions. The program included presentations on the use of oximes in the management of neuromuscular block (David Grob); enzymes in the cerebral spinal fluid (Benjamin Boshes); pathologic changes in

animals subjected to chronic potassium deficiency (Gilbert H. Glaser); and sensitivity to anticholinesterase compounds in patients subjected to radiotherapy of the thymus gland (Kermit E. Osserman).

Ann Arbor Course Directed to Practicing Physicians The postgraduate course in clinical neurology to be given under the direction of Russell N. DeJong at the University Hospital of the University of Michigan, Ann Arbor (May 7-8, 1958), will be geared to the needs of practicing physicians. History taking, diagnostic procedures, differential diagnosis, and the newer modes of therapeutic approach will be presented. Special emphasis will be placed on newer diagnostic technics and therapies. This curriculum will be supplemented by clinical presentations, motion picture demonstrations, and a review of relevant laboratory procedures.... Programs and application forms may be procured from John M. Sheldon, M.D., Director, Department of Postgraduate Medicine, University Hospital, Ann Arbor, Michigan.

Briefs Thomas W. Farmer, professor of neurology at the University of North Carolina, is on leave of absence until August 1, 1958, while he is associated with Dr. Fritz Buchthal, Institute of Neurophysiology, University of Copenhagen, Denmark.... Thomas Richard Johns has been appointed acting chief, division of neurology of the University of Virginia Hospital in Charlottesville.... H. William Gillen has been appointed chief, division of neurology of the University Medical Center, Jackson, Mississippi.

Percy Bailey

Control the major symptoms

In Parkinsonism Parsidol has proved outstandingly effective for controlling tremor and muscular rigidity, the principal impairments in this disease.[1, 2]

With Parsidol most patients show rapid, even dramatic improvement—both in major symptoms and in gait, posture, balance and speech. Side effects are minimal. Parsidol is compatible with all other antiparkinsonian drugs and its effectiveness may even be increased in combination or rotation with such preparations as atropine and dextroamphetamine.[3] Parsidol improves the patient's emotional perspective, promotes a more optimistic outlook as physical coordination and dexterity return.

Most patients can be controlled with a maintenance dosage of 50 mg. four times daily. However, more severe cases may require up to 600 mg. daily, a dosage level ordinarily well tolerated.

References: 1. Doshay, L. J.; Constable, K. and Agate, F. J., Jr.: J.A.M.A. *160*:348 (Feb.) 1956. 2. Berris, H.: J.-Lancet *74*:245 (July) 1954. 3. Timberlake, W. H. and Schwab, R. S.: N. Eng. J. Med. *247*:98 (July 17) 1952.

PARSIDOL®

hydrochloride

WARNER-CHILCOTT

Above and right are action pictures, taken from a Warner-Chilcott film study, of a parkinsonian patient before and after initiation of Parsidol therapy for major tremor.

PRODUCTS AND SERVICES

(Continued from page 22A)

STANDARD PHARMACEUTICAL NOW FEATURES FIVE PRODUCTS

Product development at Standard Pharmaceutical Company, Inc., of New York City has shown a dynamic rise. Five of the company's preparations are now in wide use: Valerianets-Dispert, chocolate-coated tablets that are odorless, non-depressant, sedative, and euphoric—indicated in cases of nervous excitement and exhaustion, anxiety and depressive states, gastrointestinal neuroses, and menopausal and menstrual molimena; Eucarbon compound charcoal tablets—for intestinal dysfunction; Transpulman, a 3 per cent solution of basis quinine in volatile oils, with 2.5 per cent camphor for intramuscular injection—for bronchitic and pulmonary involvements; Presto-boro (aluminum sulfate and calcium acetate)—for making Burow's solution U.S.P. XIV wet dressings for inflammations, swellings, and sprains; and Nucarpon compound tablets, adsorbent and carminative with a mildly laxative effect—for indigestion, hyperacidity, and flatulence.

BALDPATE, Inc.

Geo. Fleetwood 2-2131 **Georgetown, Mass.**

Located in the hills of Essex County, 30 miles north of Boston

For the treatment of psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Definitive psychotherapy, somatic therapies, pharmacotherapy, milieu-therapy under direction of trained occupational and recreational therapists.

HARRY C. SOLOMON, M.D.
Consulting Psychiatrist

GEORGE M. SCHLOMER, M.D.
Medical Director

HALL-BROOKE

An Active Treatment Hospital

A licensed private hospital devoted to active treatment, analytically-oriented psychotherapy, and the various somatic therapies.

A high ratio of staff to patients.

Large occupational therapy building with a trained staff offers complete facilities for crafts, arts and recreation. Full program of outdoor activities.

Each patient is under constant, daily psychiatric and medical supervision.

Located one hour from New York on 120 acres of Connecticut countryside.

HALL-BROOKE

Greens Farms, Box 31, Conn., Tel.: Westport, CApital 7-5105

George S. Hughes, M.D.
Leo H. Berman, M.D.
Alfred Berl, M.D.
Louis J. Micheels, M.D.
Robert Isenman, M.D.
John D. Marshall, Jr., M.D.
Peter P. Barbara, Ph.D.
Heide F. and Samuel Bernard, Administration

New York Office: 46 East 73rd Street. LEhigh 5-5155

accessory equipment
for recording
and photographing
available.

MODEL M1
ELECTROMYOGRAPH

a new, compact instrument for clinical and laboratory applications.

Write for descriptive literature and prices on:

ELECTROMYOGRAPHS
ELECTROENCEPHALOGRAPHS
STRAIN GAGE AMPLIFIERS
RECORDER PAPER
ELECTRODES
SHOCK THERAPY EQUIPMENT

- Size — 9" x 18" x 15"
- Weight — 25½ #
- Frequency Range — 10-6000 cps
- Noise Level — 6 microvolts
- Rejection Ratio — 16,000/1

MEDCRAFT ELECTRONIC CORP.

designers and manufacturers of diagnostic and therapeutic equipment for the medical profession

426 GREAT EAST NECK ROAD, BABYLON, N.Y.

TEL. MOHAWK 9-2837 ADDRESS MAIL TO BOX 1006, BABYLON, N.Y.

"I have had lots of troubles"

AFTER YEARS OF WORK, the doorway to literary success finally opened. She managed to get her novel, *Moods*, published.

It promptly flopped.

Undaunted, she wrote a second novel, which instantly turned out to be the rage of 1869. Businessmen, lawyers, housewives, everybody read and talked about *Little Women*.

Fortune had finally smiled on Louisa May Alcott. Twenty years had passed between her first writings and *Little Women*—years of privation, struggle, pain. She had worked as a maid, as a paid companion, had nearly lost her life as a Civil War nurse, had once come close to suicide.

Now world-famous, her family secure, she would write many more books. And people would love them. For, as she said, "I have had lots of troubles; so I write jolly tales."

In those words, spoke the kind of unvarnished courage without which this country would be a far poorer place. Poorer not only by Louisa May Alcott's stories, but by the accomplishments of millions. For it is human courage and character that have made America wealthy and strong. And have made America's Savings Bonds one of the world's finest investments.

170 million Americans back U.S. Savings Bonds—back them with a guarantee unmatched by any other form of saving. Your principal guaranteed safe to any amount—your interest guaranteed sure—by the greatest nation on earth. If you want *real* security, buy Bonds. Get them at your bank or through the Payroll Savings Plan where you work. And hold on to them.

PART OF EVERY AMERICAN'S SAVINGS BELONGS IN U. S. SAVINGS BONDS

The U.S. Government does not pay for this advertisement. It is donated by this publication in cooperation with the Advertising Council and the Magazine Publishers of America.

Clinical excerpts No. 2 of a series

Use of meprobamate in chronic psychiatric patients

*"What is most important . . . is that . . . no schizophrenic patient be considered as refractory to drug therapy without having had an adequate course of this drug." 'Miltown' "appears to be [a] drug of choice" in anxiety reactions and affective disorders.**

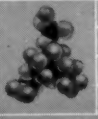
HOSPITALIZED PATIENTS

		IMPROVEMENT NOTED			
PSYCHIATRIC DIAGNOSIS	NO. CASES	MARKED OR MODERATE	PER CENT MARKED OR MODERATE	SLIGHT	NONE
Schizophrenic reaction	111	44	40%	41	26
Anxiety reaction	35	26	74%	7	2
Affective disorders	23	17	74%	3	3
Personality disorders	10	1	10%	3	6
Chronic brain syndromes	12	1	8%	8	3
TOTALS	191	89	46%	62	40

• alleviates anxiety in chronic psychiatric patients • facilitates psychotherapeutic rapport • improves disturbed ward behavior • suitable for prolonged therapy • no liver or renal toxicity reported • free of autonomic effects.

*REFERENCE
Hollister, L. E., Elkins, H., Hiler, E. G. and St. Pierre, R.: Meprobamate in chronic psychiatric patients. Ann. New York Acad. Sc. 67:789 May 9, 1957.

Miltown®



THE ORIGINAL MEPROBAMATE
DISCOVERED & INTRODUCED BY
WALLACE LABORATORIES
NEW BRUNSWICK, NEW JERSEY

CM-6371

IPRONIAZID

the psychic energizer
is available only as

MARSILID

Roche

Marsilid® Phosphate
brand of iproniazid phosphate

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc
Nutley 10, New Jersey

ROCHE®

Original Research in
Medicine and Chemistry